Novel diazaphospholidines for asymmetric synthesis

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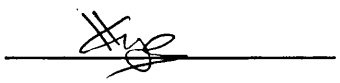
NOVEL DIAZAPHOSPHOLIDINES FOR ASYMMETRIC SYNTHESIS

Submitted by: **Heather Tye**
for the degree of PhD
of the University of Bath
1996



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DEDICATION:

I would like to dedicate this thesis to my wonderful parents. Their constant encouragement and stimulation has lead me to pursue a scientific career with an enthusiasm that I hope will remain with me for the rest of my life.

A scientist does not study nature because it is useful but because it is beautiful and if nature were not beautiful then life would not be worth living.

Henri Poinacre

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Finally I would like to thank some special people who have given me a great amount of encouragement and moral support during my PhD. Thanks to: Lynda Linney for not only being a good friend but also for helping me with the molecular modelling work; Veronica Paget for being a shoulder to cry on during the hard times and a shoulder to lean on during the drunken ones; lastly and most certainly not least Paul Comina (my future husband) for all his love and for believing in me when it mattered most.

ABBREVIATIONS

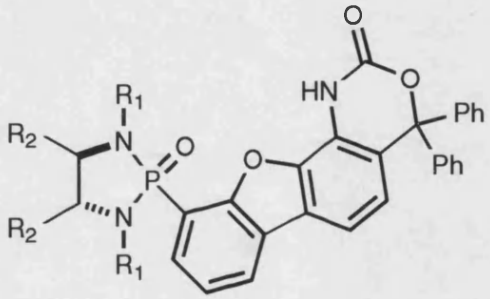
BMS	Borane Dimethyl Sulfide Complex
BSA	N,O-bis-(trimethylsilyl)-acetamide
Bn	Benzyl
Bu	Butyl
CAC	Critical Association Constant
CAM	Ceric Ammonium Molybdate Solution
Cbz	Carbonyl benzyloxy
CI	Chemical Ionisation
COSY	Correlation Spectroscopy
DABCO	Diaza Bicyclooctane
DCM	Dichloromethane
d.e.	Diastereomeric Excess
DEPT	Distortionless Enhancement by Polarisation Transfer
DG	*ortho* Directing Group
4-DMAP	4-Dimethylamino Pyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic Acid
DPPA	Diphenyl Phosphoryl Azide
e.e.	Enantiomeric Excess
EI	Electron Impact Ionisation
ent	Enantiomer of
$Eu(hfc)_3$	Tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]Europium(III) Complex
FAB	Fast Atom Bombardment
FTIR	Fourier Transform Infrared Spectroscopy
HMPA	Hexamethyl Phosphoramide
HMPT	Hexamethyl Phosphorus Triamine
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IPA	Isopropyl Alcohol
iPr	Isopropyl
IR	Infrared Spectroscopy
LAH	Lithium Aluminium Hydride
LDA	Lithium Diisopropylamine
*m*CPBA	*meta* Chloro Perbenzoic Acid
MSH	Mesitylene Sulfonyl Hydroxylamine
n-Bu	normal-Butyl

NBS	N-Bromo Succinamide
nOe	Nuclear Overhauser Effect
NOESY	Two Dimensional nOe Spectroscopy
NMR	Nuclear Magnetic Resonance Spectroscopy
N-t-Boc	N-tertiary Butoxy Carbonyl
Nu	Nucleophile
OAc	O-Acyl
PMA	Phospho Molybdic Acid
p-Tol	*para*-Tolyl
RP	Reverse Phase
s-Bu	secondary-Butyl
TBDPS	tertiary-Butyl Diphenyl Silyl
t-Bu	tertiary-Butyl
Tf	Triflate
THF	Tetrahydrofuran
t.l.c.	Thin Layer Chromatography
TMEDA	Tetramethyl Ethylene Diamine
TMS	Trimethyl Silyl
Ts	Tosyl

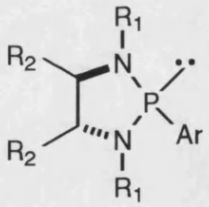
ABSTRACT

The synthesis of two families of novel, enantiomerically pure, diazaphospholidines derived from C_2-symmetric diamines is described.

The first section of the thesis deals with P(V)-diazaphospholidine oxides and their use as cleft receptors for the recognition of N-t-Boc amino acid derivatives. A moderate degree of enantioselectivity in binding N-t-Boc-D and L-alanine was achieved. Initial attempts to use the cleft receptors as catalysts in the asymmetric synthesis of amino acid derivatives is also discussed.



The second section of the thesis describes the synthesis of a number of P(III)-diazaphospholidines and their application as ligands for palladium in the allylic substitution reaction. Allylic alkylations and aminations were carried out with moderate to good enantioselectivities for a range of substrates. The possibility of applying this methodology to the asymmetric synthesis of novel amino acids is also briefly described.

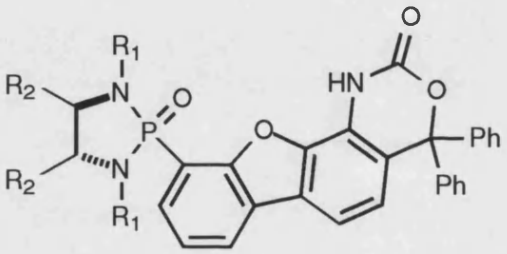


General Introduction

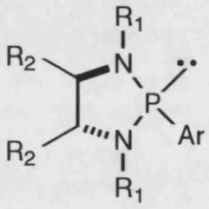
GENERAL INTRODUCTION:

This Thesis describes the synthesis and application of a novel class of chiral diazaphospholidine compounds derived from C_2-symmetric 1,2-diamines. Two main types of diazaphospholidine have been studied: the P-(V) oxides (Section 1) have been employed in the synthesis of chiral cleft receptors for amino acid derivatives; the P-(III) phosphines (Section 2) have been utilised as ligands for palladium catalysed allylic substitution reactions (see fig. 0.1).

Fig. 0.1:



Chiral Cleft Receptors
for Amino Acid Recognition

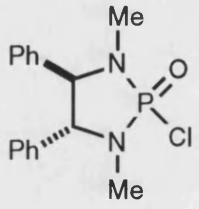


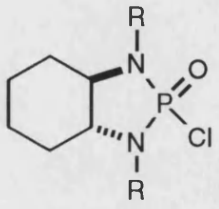
Chiral Ligands for
Allylic Substitution Reactions

Examples of chiral P-(V) and P-(III) diazaphospholidines are relatively few, particularly in the case of the P-(III) compounds. A brief overview of pertinent literature examples will be given here.

P-(V) Diazaphospholidine Oxides

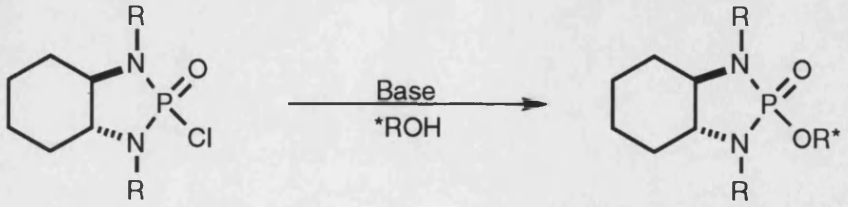
Fig. 0.2:





R = Me, iPr

Scheme 0.1:



Diastereomeric Mixture

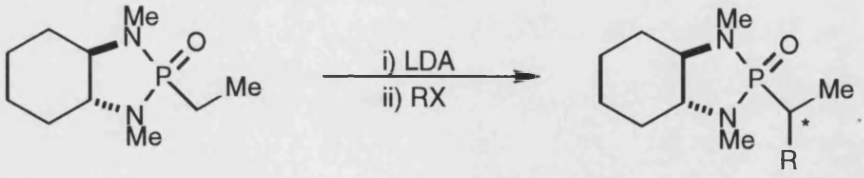
Alexakis and co-workers have employed chloro diazaphospholidine oxides, derived from the reaction between C_2-symmetric diamines and phosphorus oxychloride, as chiral derivatising

agents for chiral alcohols and thiols (see fig. 0.2).[1] The alcohols/thiols react to form diastereomers which can be analysed using NMR to determine the optical purity of the sample (see scheme 0.1).

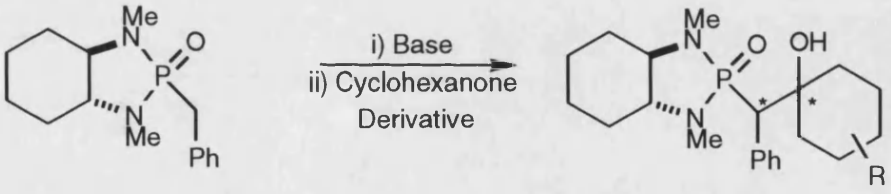
Hanessian has reported a number of applications of chiral diazaphospholidines as auxiliaries in asymmetric synthesis. For example they have been employed as a chiral anion source in asymmetric aldol reactions with cyclohexanone derivatives and in reactions with alkyl halides (see schemes 0.2 and 0.3).[2, 3]

Schemes 0.2 and 0.3:

Chiral Anion Source

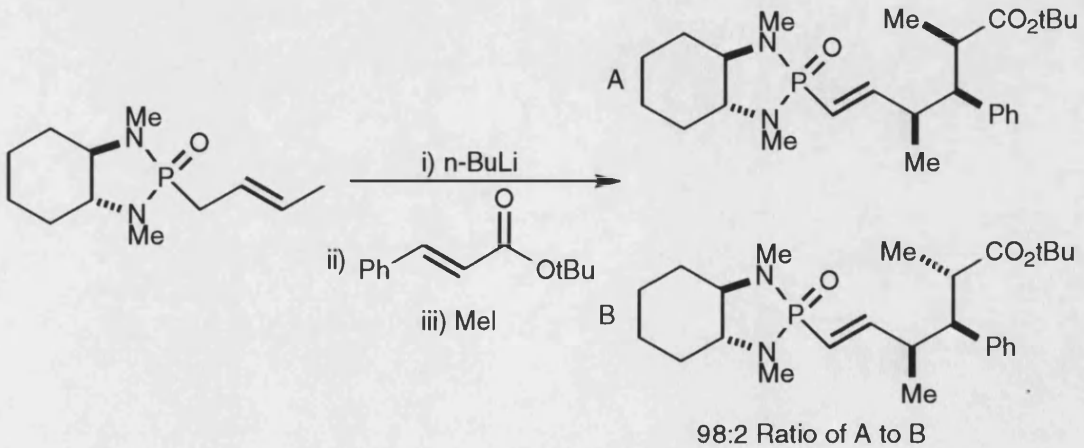


Aldol Reaction



Such auxiliaries have also been used to give a high degree of diastereoselectivity in conjugate addition reactions where complete *anti* selectivity was achieved in the 1,4-addition step and a 98:2 diastereoselectivity occurred in the subsequent enolate quench with methyl iodide (see scheme 0.4).[4]

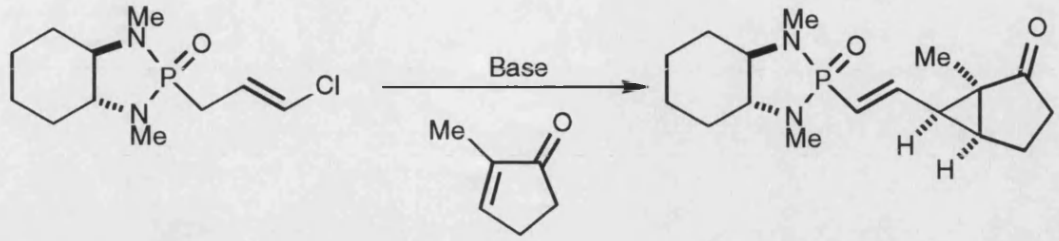
Scheme 0.4:



98:2 Ratio of A to B

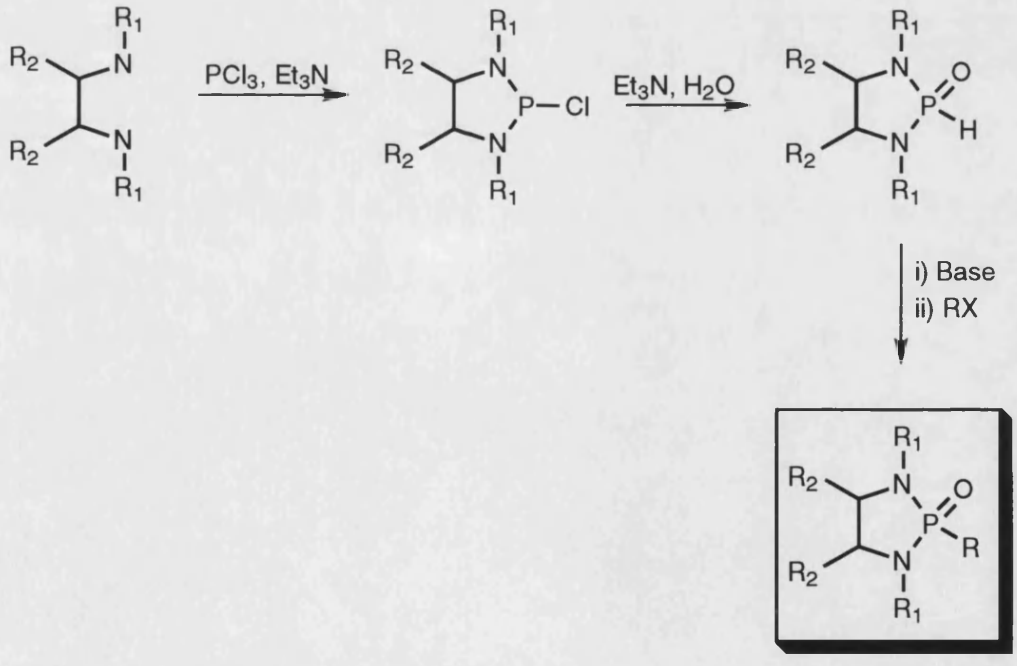
A similar result was achieved in cyclopropanation reactions giving exclusively one isomer of the tetra substituted cyclopropane product when the E-isomer of the vinyl chloride precursor was employed (see scheme 0.5).[5]

Scheme 0.5:



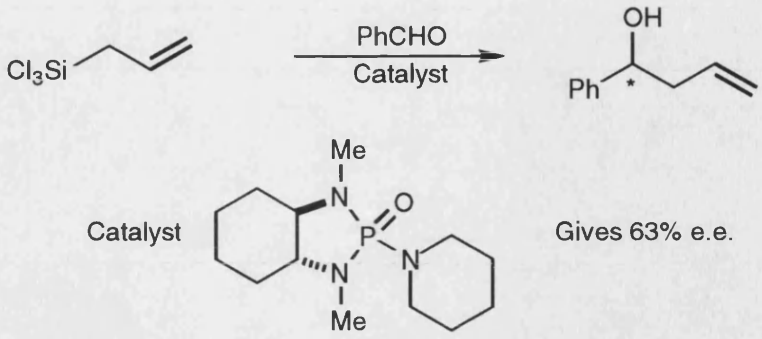
Diazaphospholidine oxides of the type used by Hanessian can be readily synthesised from the corresponding diamines in a three step procedure developed by Spilling and co-workers.[6] Reaction of the diamine with phosphorus trichloride gives a chloro diazaphospholidine which can be oxidised in the presence of water and then derivatised at phosphorous using a strong base and a variety of alkyl halides (see scheme 0.6).

Scheme 0.6:



Denmark has recently demonstrated the use of amino diazaphospholidine oxides as catalysts for the asymmetric allylation of benzaldehyde with a reasonable degree of enantioselectivity (see scheme 0.7).[7] The diazaphospholidine P=O is believed to act as a Lewis base and interact with the trichlorosilyl allyl species to promote its reaction with benzaldehyde.

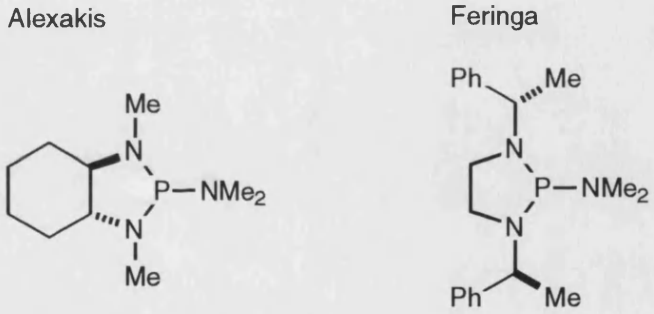
Scheme 0.7:



P-(III) Diazaphospholidines

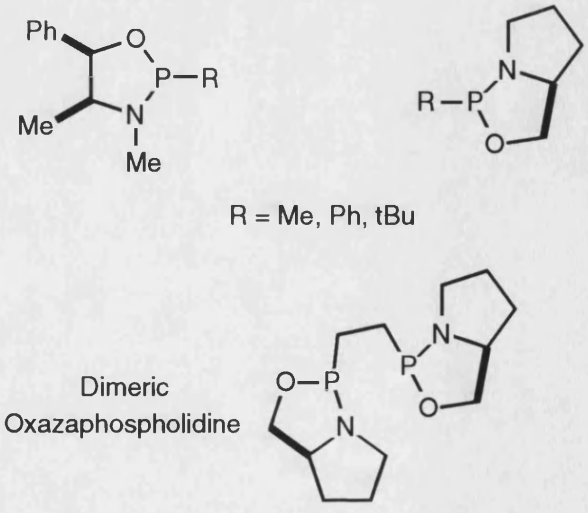
Only two examples of chiral diazaphospholidines have appeared in the literature and both are amino derivatives which have been employed as chiral derivatising agents for the determination of enantiomeric purity of alcohols (see fig. 0.3).[1, 8]

Fig. 0.3:



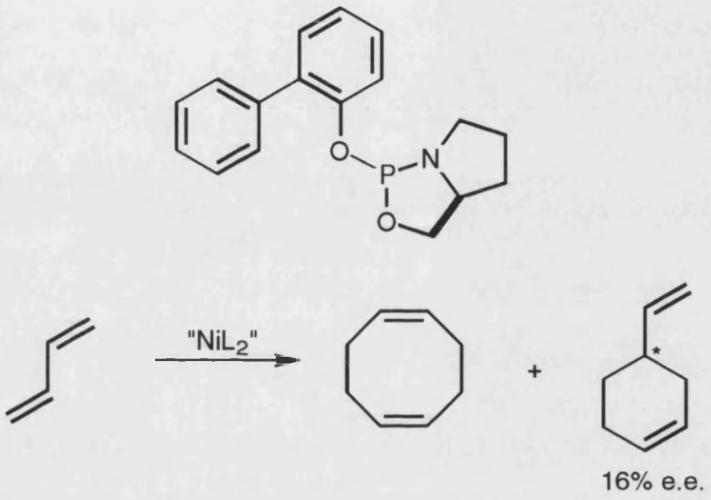
Most other literature examples refer to the structurally related oxazaphospholidines derived from chiral amino alcohols. Richter reported the direct synthesis of a number of oxazaphospholidines derived from prolinol or ephedrine and the corresponding bis-amino phosphines (see fig. 0.4).[9]

Fig. 0.4:



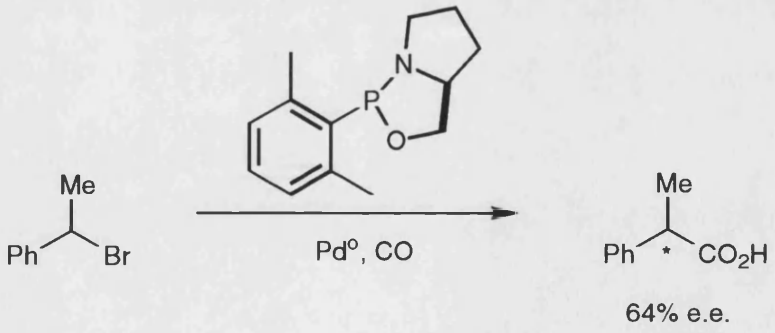
Buono has also reported a series of prolinol derived compounds which have been applied to asymmetric synthesis.[10, 11, 12] In 1987 he reported their use as chiral ligands for the nickel catalysed cyclodimerisation of butadiene to give 4-vinyl cyclohexene, albeit with poor enantioselectivity (max. 16%, see scheme 0.8).

Scheme 0.8:



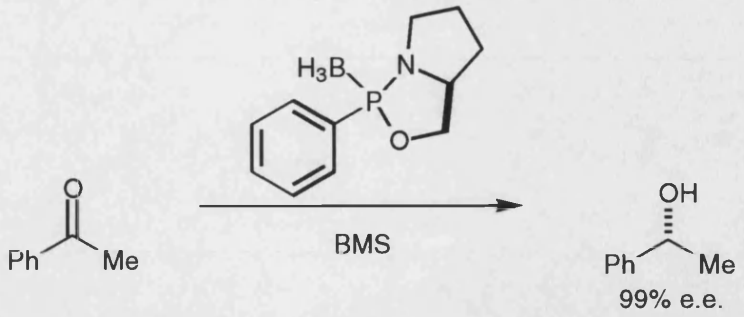
Later he reported the use of similar ligands for the palladium catalysed asymmetric carbonylation of α-methylbenzyl bromide but again with only moderate selectivity (up to 64% e.e., see scheme 0.9).

Scheme 0.9:



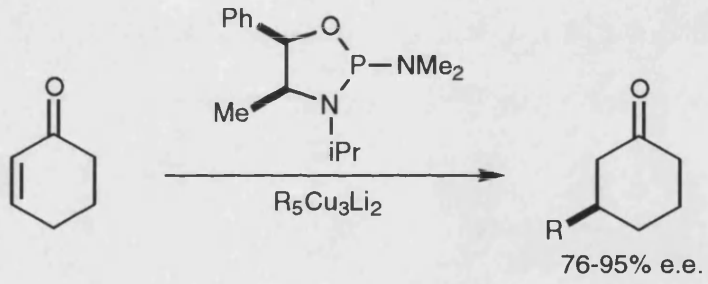
Most recently he reported the application of a borane complex (of an oxazaphospholidine) in the asymmetric reduction of prochiral ketones giving enantioselectivities of up to 99% when stoichiometric amounts of the complex were used (see scheme 0.10).

Scheme 0.10:



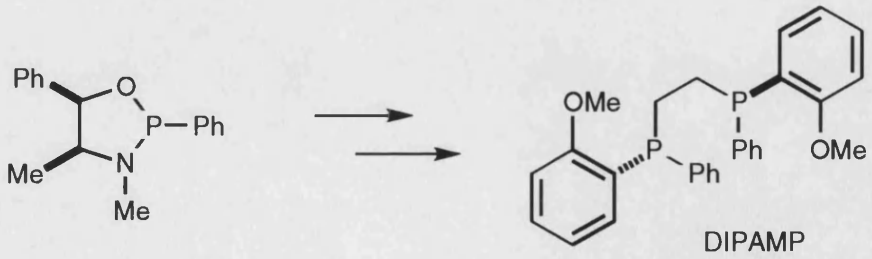
Alexakis has reported the application of amino oxazaphospholidines, derived from ephedrine, to catalyse the conjugate addition of higher order cuprates to cyclohexenones with moderate to good enantioselectivities (see scheme 0.11).[13]

Scheme 0.11:



Genet has also utilised an ephedrine based oxazaphospholidine as a chiral intermediate in the asymmetric synthesis of the chiral diphosphine ligand DIPAMP (see scheme 0.12).[14]

Scheme 0.12:



It seems logical that diazaphospholidines could be used in many similar applications and to some advantage since they are not chiral at phosphorus and thus separation of diastereomers, which has been a problem in the synthesis of oxazaphospholidines, would not be necessary.

Section 1

SECTION 1:
CHAPTER 1: INTRODUCTION TO MOLECULAR RECOGNITION

General Principles of Molecular Recognition

The field of molecular recognition has its roots deep in the study of biological systems. The tertiary structure and function of complex molecules such as DNA and enzymes rely strongly on specific, non covalent, inter and intramolecular interactions such as hydrogen bonding, ion pairing and charge transfer processes. In recent years the translation of these concepts to the synthetic arena has been achieved with increasing success.

Such synthetic molecular recognition systems have been put to use in a wide variety of applications ranging from ion sequestering agents, through chiral stationary phases for HPLC to artificial enzymes and self replicating molecules. However, before a synthetic molecular recognition system can be designed the underlying principles governing receptor-substrate interactions must be considered.

The Concept of Preorganisation and Complimentarity

The concepts of preorganisation and complimentarity were first introduced by D. J. Cram.[15] The binding interaction between substrate and receptor will be significantly enhanced if the receptor topography is inherently complimentary to that of the substrate. Complimentarity is achieved when the desired interactions (such as hydrogen bonds) can be achieved without adverse clashing interactions and cavities occurring upon complexation. Thus receptor design is not just a problem of providing the appropriate functional groups for intermolecular interaction but also of placing them in appropriate positions within the molecular architecture of the receptor.

The concept of preorganisation is more complex and stems from an understanding of the thermodynamic aspects involved upon receptor-substrate interaction.[16] The free energy associated with the formation of a receptor-substrate complex is given by the equation:

$$\Delta G = \Delta H - T\Delta S$$

(Where G is the free energy, H is the enthalpy, S is the entropy and T is the temperature).

The overall free energy of complexation can be broken into six components all of which will contribute either positively or negatively to complex formation:

1) Any bimolecular process to form a single complexed species is entropically unfavourable due to the loss of translational and rotational degrees of freedom in both receptor and substrate.

2) Loss of internal rotational degrees of freedom in both receptor and substrate also leads to a decrease in entropy.

3) Favourable solvent effects resulting from the disordering of solvent molecules (previously complexed to receptor and substrate) serve to increase entropy.

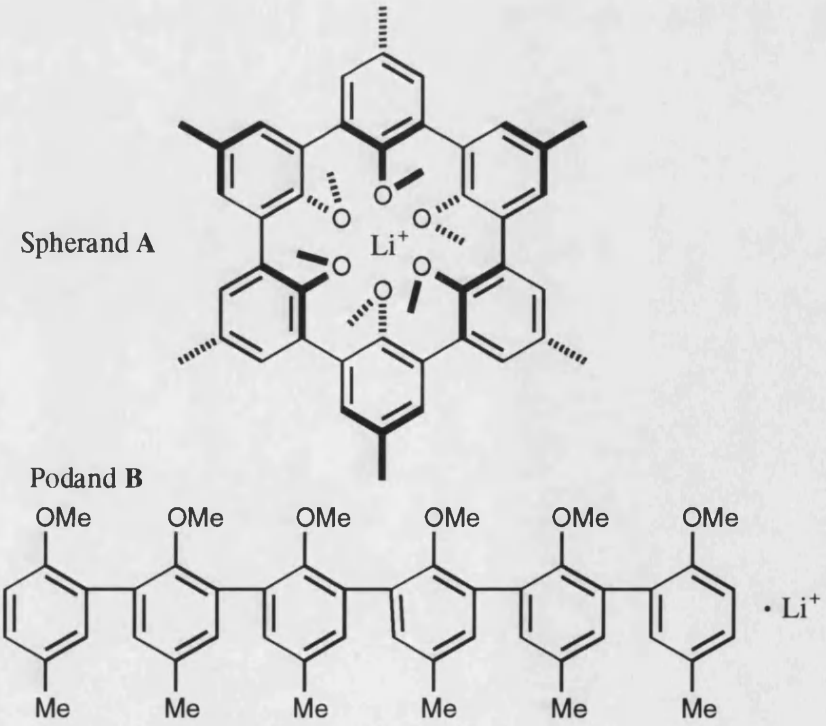
4) Favourable binding interactions between pairs of functional groups in receptor and substrate affect the enthalpy.

5) Total conformational strain upon complexation affects the free energy of the complex.

6) Differences in Van der Waals energies between bound and free states due to repulsions and cavities in the complex also affect the free energy.

Designing complimentary receptors will largely serve to control the favourable binding interactions (4), the conformational strain (5) and the Van der Waals terms (6). Preorganisation enables minimisation of entropy losses resulting in a reduction in internal rotational degrees of freedom (2).

Fig. 1.1:



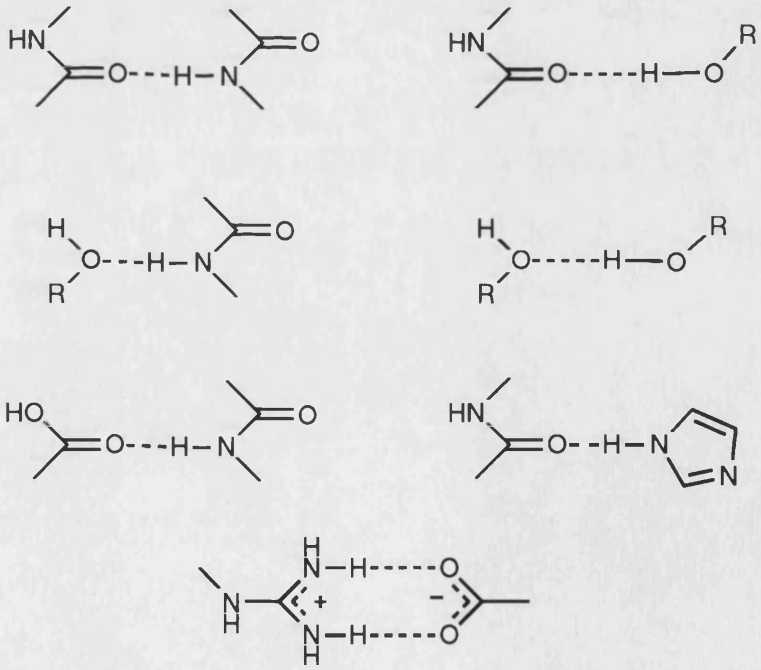
If the receptor is designed to exist in a minimal number of conformations suitable for substrate binding then it is said to be preorganised for binding (the number of internal degrees of freedom, in the receptor, lost upon binding will be at a minimum). An impressive example of the difference that preorganisation can make to the binding free energy was demonstrated by Cram for the ionophores **A** and **B** (see fig. 1.1).[15]

Spherand **A** exists in a single low energy conformation which is ideally suited for binding Li^+ in the cavity. Podand **B** exists in more than 1000 different low energy conformations only 2 of which are suited to Li^+ binding. The energy cost of organising **A** for binding was paid in its synthesis. In the case of **B** this energy cost has to be paid during the binding process which equates to a large difference in binding free energy of 17 kcal mol^{-1} between the two cases.

It is, however, useful to bear in mind that a receptor which is completely rigid may suffer from a loss in complimentarity and will most certainly not bind to a range of substrates effectively, thus a balance must be struck.

Hydrogen Bonding Interactions

Fig. 1.2:

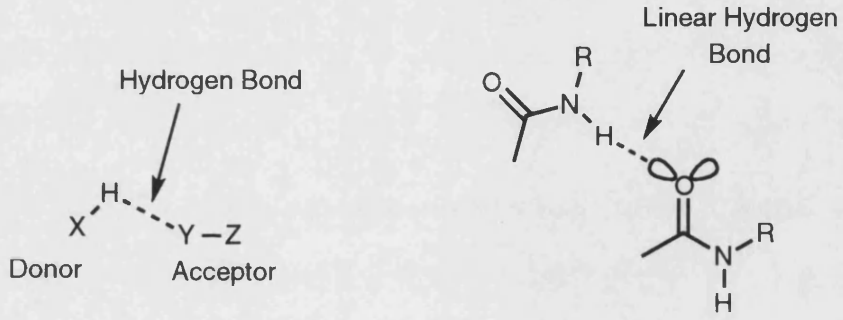


Hydrogen bonds are perhaps the most prevalent intermolecular interactions observed in nature and have been used to good effect in synthetic receptors. Their use is favoured for several reasons: firstly a wide range of functional groups are capable of exhibiting hydrogen bonding and all of these are available in the synthetic organic chemists repertoire (see fig. 1.2

for some examples); secondly, because they are prevalent in nature, the properties of hydrogen bonds are well understood and thus the desired receptor can be easily tailored to meet the needs of the chemist.

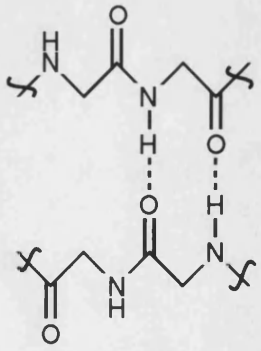
Hydrogen bonding involves the participation of three interaction mechanisms; coulombic electrostatic interactions, dispersive forces and charge transfer processes. The coulombic interaction is the major factor and relates to the acidity of the donor X-H and the basicity of the acceptor Y.[17] For example any functional group with a labile proton (OH, NH, HF etc.) will hydrogen bond to an electronegative group (C=O, C=N, RO, etc.). The strength of the interaction will thus be determined by the size of this coulombic interaction.

Fig. 1.3:



Another important property of the hydrogen bond is the high degree of directionality achieved in such interactions (see fig. 1.3). The geometry of the donor hydrogen is controlled by the steric constraints imposed by the donor group X. Equally the charge distribution on Y is controlled by the lone pair geometry and this therefore results in the formation of a linear hydrogen bond in a specific direction. An excellent example of this effect is observed for hydrogen bonds formed between the amide groups of peptide chains in β-sheets (see fig. 1.4).

Fig. 1.4:

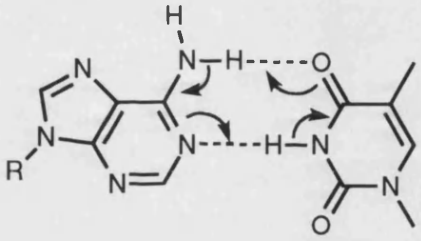


Since the geometry of hydrogen atoms and lone pairs in different functional groups is well understood, this directionality of hydrogen bonding has been used to great effect in synthetic

receptor-substrate systems (for some examples see review articles by H. J. Schneider[17], J. Rebek Jnr.[18], and C. S. Wilcox[19]).

Many hydrogen bonded systems rely on more than one interaction to hold the receptor-substrate complex together. Often the strength of the overall set of interactions is observed to be greater than the sum of the individual components (even when other factors such as those discussed earlier are taken into account). In some cases hydrogen bonds can combine in a manner where they are observed to reinforce each other, this effect is known as π-cooperativity and plays an important role in the hydrogen bonding of DNA base pairs A-T and C-G (see fig. 1.5).[20] When hydrogen bond donors and acceptors are arranged alternately in a cyclic array a flow of electrons between the π-bonding and antibonding orbitals is possible and this serves to strengthen the interaction.

Fig. 1.5:



π-Cooperativity Reinforces Hydrogen Bonding

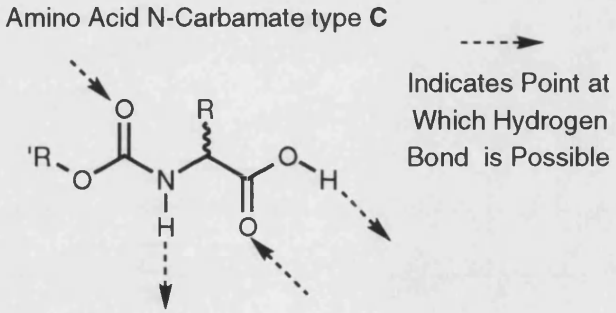
One final important aspect to consider is the effect that solvent can have on the strength of receptor-substrate interactions. The entropic effect of solvent disorganisation upon binding has been briefly discussed but the extent of this effect is largely governed by the nature of the interactions occurring between the solvent and the receptor/substrate. The choice of solvent can strongly influence the extent of binding achieved, particularly for hydrogen bonded systems. If the solvent is capable of forming hydrogen bonds then it will act as a competitive inhibitor to binding.[17, 21] In systems where the receptor and substrate are weakly solvated, for example in chloroform or carbon tetrachloride, the extent of binding is much greater than for systems where strong solvation occurs, for example in DMSO, methanol, THF or water. Thus the strongest hydrogen bonds have been observed when non-polar solvents such as carbon tetrachloride have been used. (Note: chloroform can hydrogen bond weakly due to its dipole moment. This results in a reduction in binding constant (K) of approximately $1M^{-1}$ compared to cases where carbon tetrachloride is used as solvent.)

Having outlined the important factors involved in molecular recognition processes the design of the receptors employed in this project will now be discussed.

Design of Cleft Receptors for the Recognition of Amino Acid Derivatives

The initial goal of the project was to design and synthesise a cleft receptor for amino acid N-carbamates of type **C** (see fig. 1.6). Cleft receptors are concave host molecules which enclose their substrate in a cleft and interact with it from several converging directions. This avoids the use of linear, parallel vectors for interaction and thus increases the binding efficiency over that of flat surfaces.[17] The cleft's concave nature also reduces the probability of self complexation, since it is unlikely that a molecule of the receptor will fit easily into the cleft of another. A variety of cleft receptors have been used to bind amino acid derivatives and other small molecules with great success (see fig. 1.7).[22, 23, 24]

Fig. 1.6:



Amino acid N-carbamates of type **C** were considered to be capable of forming three hydrogen bonds, the first two involving the acid group and the third involving either the carbamate N-H or carbonyl group (see fig. 1.6).

It was envisaged that an additional π-cooperative effect could be achieved if a *cis* amide or *cis* carbamate were employed as the complimentary group to the acid. Owing to the inherent propensity of amides and carbamates to exist as the *trans* isomer such a *cis* conformation would have to be achieved by placing the amide or carbamate in a ring (see fig. 1.8). The final hydrogen bond could be achieved using either a *trans* amide or a phosphonamide to coordinate to the carbamate N-H on the amino acid derivative.

Fig. 1.8:

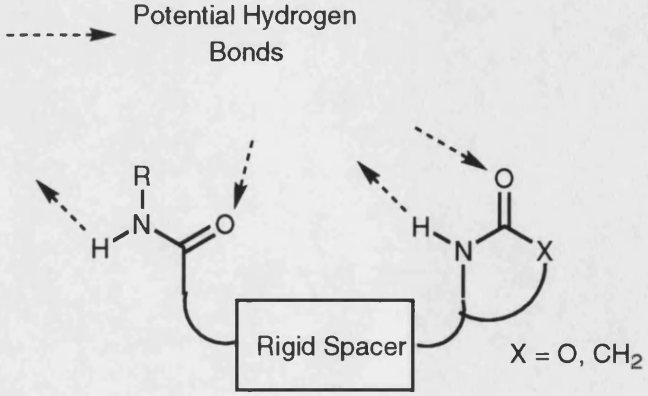
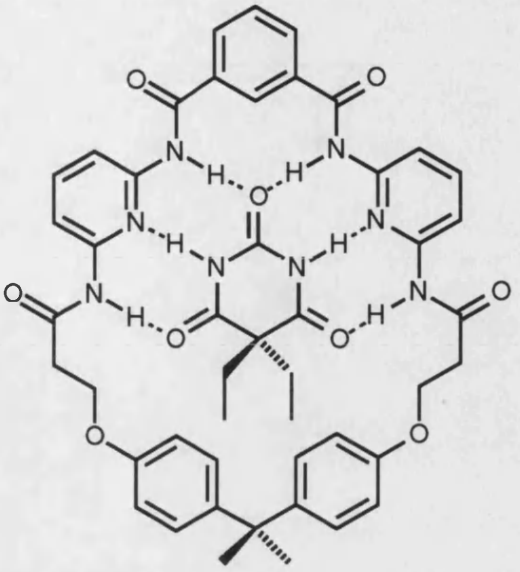
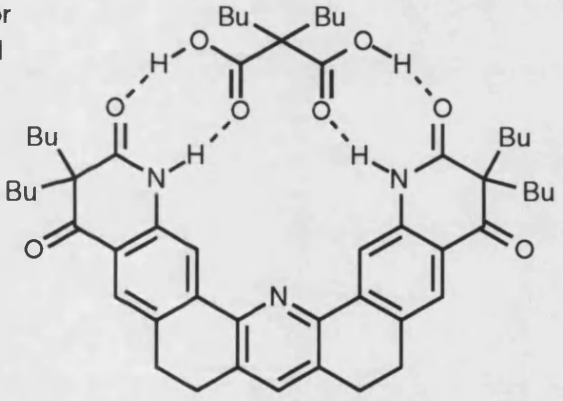


Fig. 1.7:

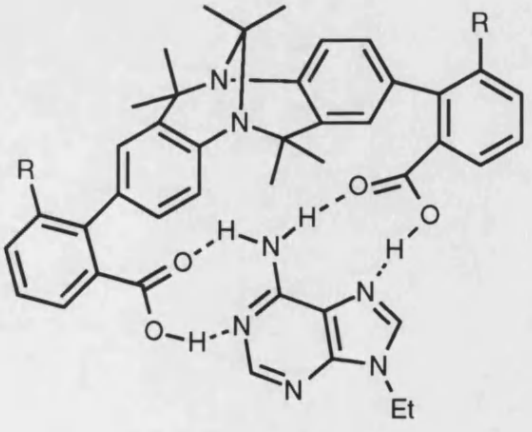
Hamilton's Receptor for Barbital



Moran's Receptor for Dibutyl Malonic Acid



Wilcox's Receptor for 9-Ethyl Adenine

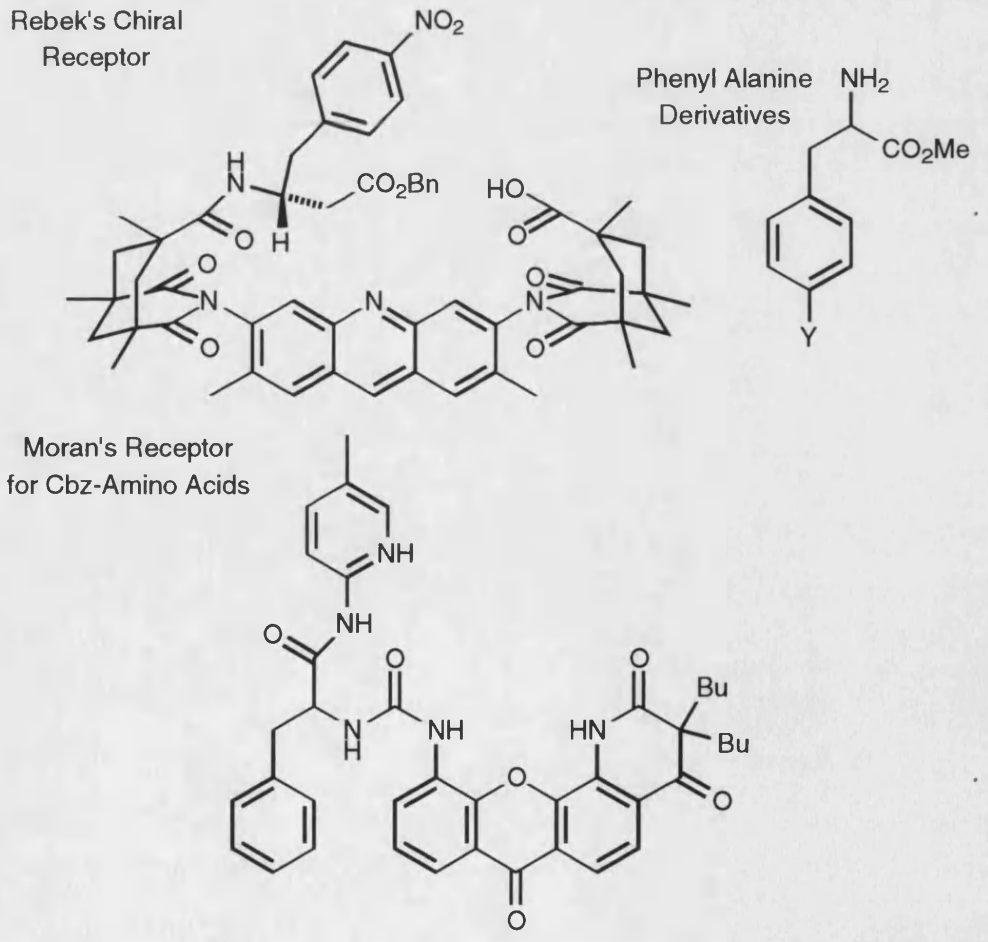


The above functional groups would then have to be placed in the correct spacial orientation suitable for binding. This could be achieved by using a rigid spacer unit to hold the functional groups in a conformation that was preorganised for binding to the amino acid derivative. This would have to be achieved in a manner that enabled a degree of flexibility so that binding to a variety of substrates could be tolerated (the freedom of the *trans* amide or phosphonamide to rotate was expected to satisfy this requirement).

Chiral Cleft Receptors

A further goal of the project was to attempt enantioselective binding and thus distinguish between the enantiomers of amino acid N-carbamates. Some success at using cleft receptors to this end has been achieved in recent years (see fig. 1.9) but the area is still very much in its infancy. For example, Rebek has reported a cleft receptor which was employed as a chiral solvating agent for phenyl alanine derivatives and Moran has synthesised a cleft capable of binding Cbz-protected amino acids with enantioselectivities of up to 20%.[19, 25, 26]

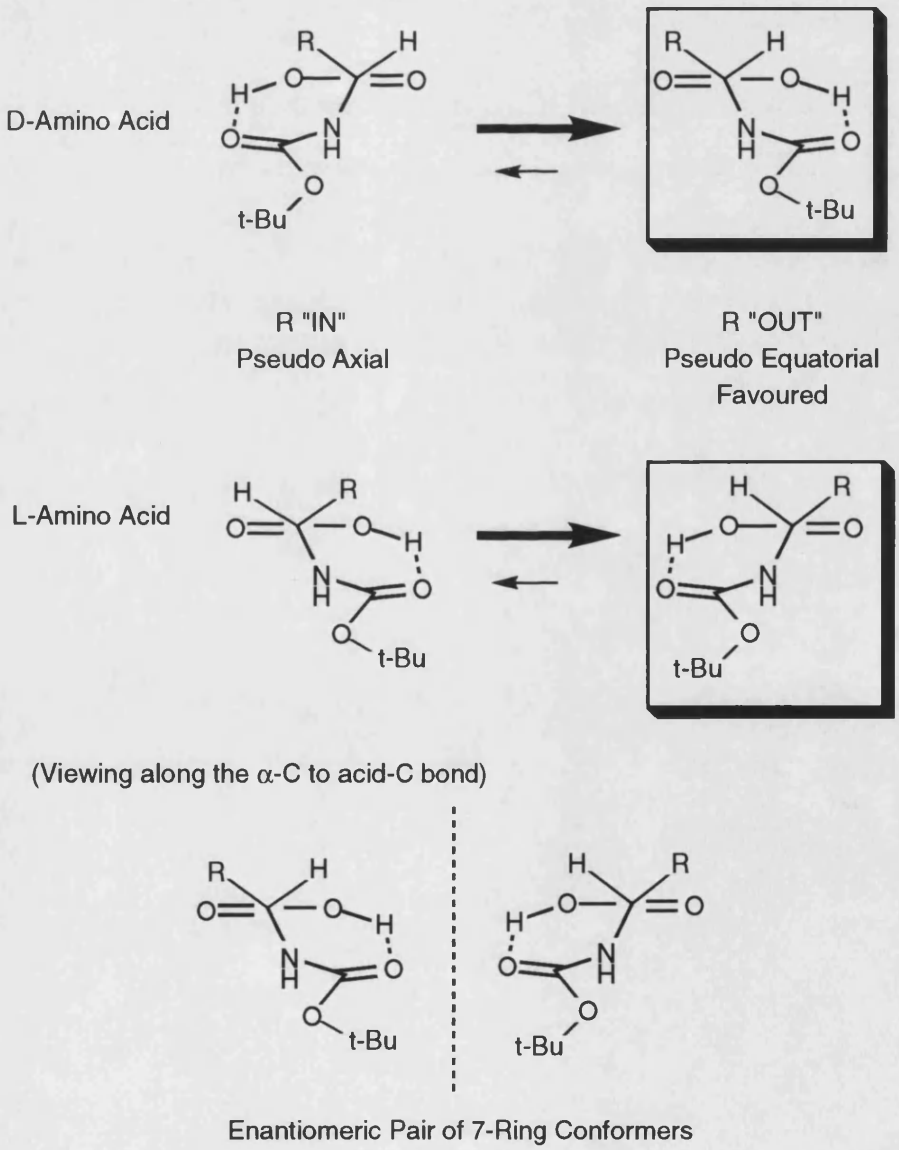
Fig. 1.9:



In order to investigate a means of differentiating the amino acid N-carbamate enantiomers an understanding of their solution phase conformations was required. Two possible low energy

conformations arise from a hydrogen bond interaction between the acid O-H and the carbamate C=O to form a seven membered ring (see fig. 1.10).[27] The two conformers can interconvert by breaking of the hydrogen bond, rotation of the acid and carbamate groups and reformation of the hydrogen bond. For a given amino acid one of the conformers is expected to be more stable than the other because of steric interactions involving the side chain R. When R exists in a *pseudo* equatorial orientation (pointing out of the ring) the steric interactions are minimal. However, when R is in a *pseudo* axial orientation (pointing into the ring) the steric interactions are greater and this conformation is disfavoured. The two enantiomers of the amino acid N-carbamates would thus favour cyclisation to the seven membered ring conformation such that the steric interactions of their respective R groups were minimised and this would result in the formation of enantiomeric seven ring conformers.

Fig. 1.10:

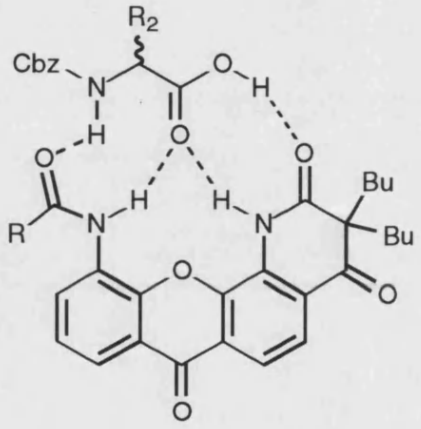


From the above analysis it is clear that enantioselection could be achieved by binding the amino acid N-carbamates in a manner which mimics the seven ring conformation. If the receptor were designed so that only one of the enantiomers could bind in its favoured conformation (with the R group in a *pseudo* equatorial orientation) then some degree of enantioselectivity would hopefully be achieved.

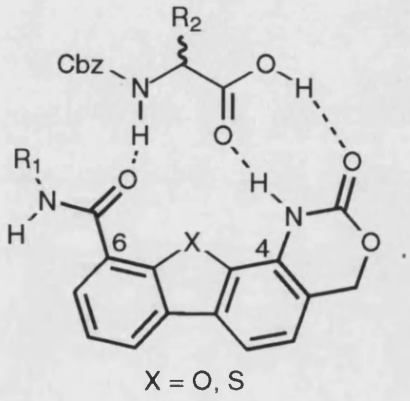
Predictions from Molecular Modelling Studies

Comparison with similar molecular clefts and molecular modelling studies (see Appendix Chapter 1) lead to the proposal of using dibenzothiophene (and indeed dibenzofuran) as the rigid spacer unit in the receptors.[26]

Fig. 1.11:



Moran's Receptor for Cbz-Amino Acids



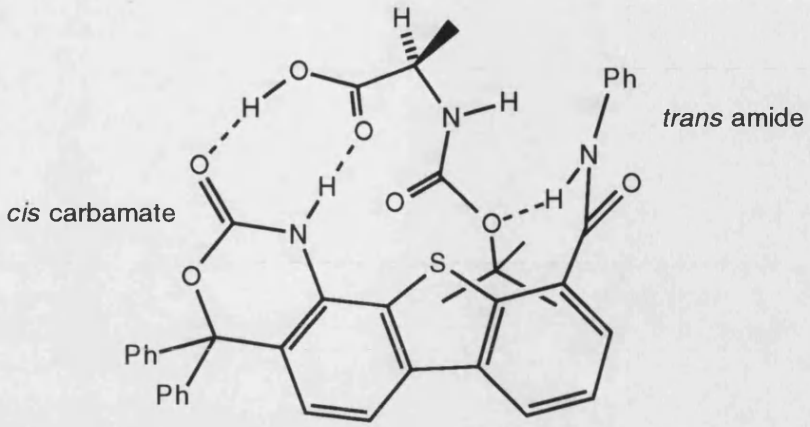
X = O, S

Proposed Receptor has a Larger Bite Angle and Should Exhibit a Different Binding Mode

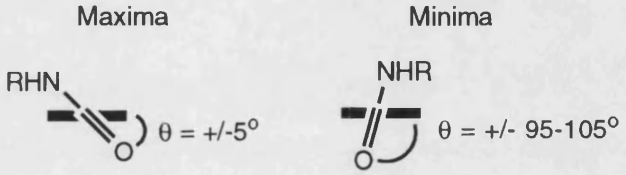
An amino acid receptor designed by Moran (see fig. 1.11) was unable to bind amino acids entirely within the cleft (i.e. not in the manner desired in this project) due to the narrow bite angle provided by the aromatic spacer.[26] The cleft size could be increased by using a rigid spacer with a wider bite angle, such as dibenzothiophene/dibenzofuran, which would force the substituents at the 4 and 6-positions to be further apart in space.[28]

Molecular Mechanics calculations carried out using Macromodel (see fig. 1.12) demonstrated that the proposed cleft receptors could indeed be involved in a low energy binding interaction with an amino acid N-carbamate. The *cis* carbamate was observed to bind to the acid group as predicted. Surprisingly the lowest energy conformation found in this analysis also exhibited an unusual hydrogen bond between the *trans* amide N-H and the carbamate C-O-Bu group. However, a slightly higher energy conformer was found where the expected *trans* amide C=O to carbamate N-H hydrogen bond was observed.

Fig. 1.12:



Rotation of the Amide



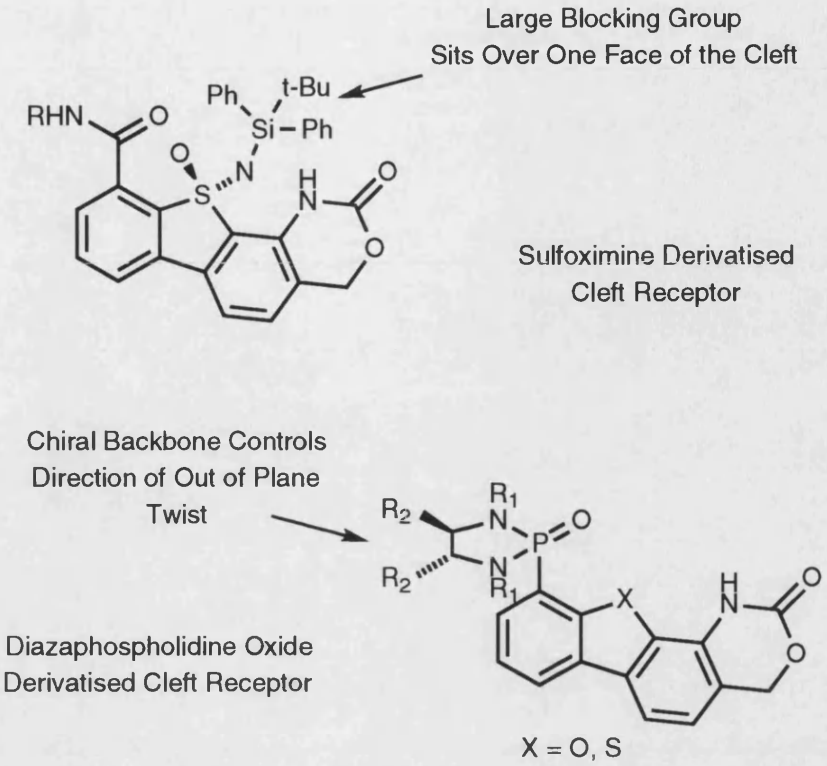
The conformation with the R = Me group in a pseudo equatorial orientation was observed (as discussed earlier, this would correspond to the 7-ring conformation with the R group positioned outside the ring in a favourable orientation). Also notable was the fact that the *trans* amide was rotated away from the aromatic plane. A study of the barrier to rotation of the *trans* amide showed maxima where the amide was observed to be virtually parallel to the aromatic plane and minima when it was in a perpendicular orientation (see fig. 1.12 and Appendix Chapter 1).

The above observations highlighted the possibility that enantioselectivity could be achieved if the direction in which the amide was able to rotate could be restricted or a steric blocking group could be introduced at the centre of the cleft to disfavour binding of one of the enantiomers.

Stereoselection Using Sulfoximines or Diazaphospholidine Oxides

Derivatisation of the proposed receptor, containing the dibenzothiophene spacer, as a chiral sulfoximine would enable the introduction of a sterically demanding group at the centre of the cleft (see fig. 1.13). From the above discussion it seems clear that such a group should significantly disfavour binding of the amino acid N-carbamate enantiomer which would prefer to position its side chain (R) on the same side as the large sulfoximine N-substituent.[29]

Fig. 1.13:



The other possibility for providing a means of enantioselectivity lies with the restricted rotation of the amide group on the receptor. This could in theory be achieved by employing a chiral diazaphospholidine oxide in place of the *trans* amide (see fig. 1.13). If the diazaphospholidine oxide were derived from a C_2-symmetric diamine (see earlier discussion on similar diazaphospholidine oxides) then the direction of rotation of the P=O group out of the aromatic plane could be controlled by the chiral backbone and thus axial chirality in the receptor would be induced. This control over the binding conformation of the receptor should then provide a means for enantioselective binding as discussed above.

Assessing the Strength of Binding Interactions

The final consideration that has to be made when designing a receptor is that it must be possible to measure the strength of the desired binding interaction by use of one or more analytical techniques. In this case, where the proposed receptor employs hydrogen bonding interactions to bind to the substrate, the use of ^1H NMR is perhaps the most appropriate. Upon binding, any protons involved in hydrogen bonding would experience a deshielding effect resulting in a down-field shift of the signal in the proton NMR spectrum. The size of the shift is related to the strength of the interaction and provides a measure of the extent of receptor to substrate binding.

NMR Titration Experiment and Theory

The use of NMR titration techniques in host-guest chemistry is becoming increasingly important as a means of determining binding constants (K) and binding free energies (ΔG).[30, 31, 32] For host-guest systems which employ hydrogen bonding for complex stabilisation the choice of solvent for titration techniques is important since (as discussed earlier) polar solvents such as MeOH, DMSO, and THF compete for hydrogen bonding sites and thus weaken the host-guest interaction.

There are two important parts to an NMR titration experiment. The first is the measurement of the Critical Association Constant (CAC) of the host in the chosen solvent (usually $CDCl_3$). This determines the concentration below which no appreciable self association of the host occurs. The second is the titration of host against varying amounts of guest (or the reverse) to assess the degree of association of host with guest. Before discussing these two aspects it is important to understand the principles behind the titration experiment.

Equation 1.1:

$$H + G \underset{k^{-1}}{\overset{k^{1}}{\rightleftharpoons}} \{H\text{-}G\}$$

H = Host
G = Guest
{H-G} = Complex

Rate of exchange $k = k^1 + k^{-1}$

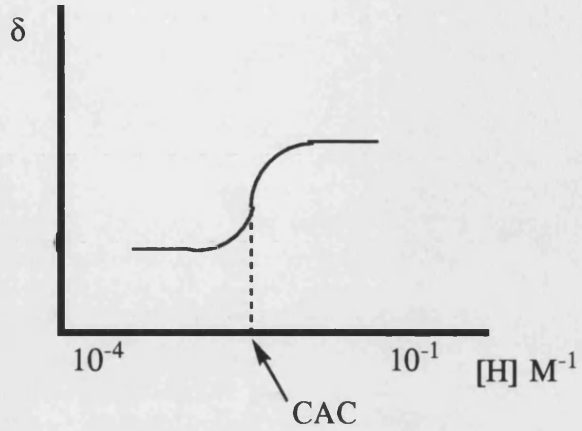
The complexation process can be considered as an equilibrium between the individual host or guest molecules and the complex (equation 1.1). If the equilibrium process is slow on the NMR time scale then two sets of signals will be seen in the NMR spectrum; one corresponding to uncomplexed host and guest and the other to the complex. If, however, the equilibrium is fast on the NMR time scale only one average signal will be observed in the spectrum. The position of this signal will shift according to the degree of complexation occurring. Comparison with literature examples suggests that the type of host-guest system proposed in this project would be expected to operate under fast exchange conditions hence only this case will be discussed further.[33]

Determination of CAC

If a set of NMR spectra for the host are measured for a range of host concentrations then a determination of the CAC can be made. A plot of the chemical shift value for a proton involved in the binding interaction (for self association) against the concentration of host will appear as shown (plot 1.1).[34] At the CAC the chemical shift will begin to alter as self association starts to occur and this is seen as a point of inflexion on the curve. At host concentrations below the CAC no appreciable self association will occur and subsequent

titration measurements should therefore be carried out at concentrations below that of the CAC.

Plot 1.1:



The Titration Experiment

The equilibrium equation (equation 1.2) for the host guest interaction is shown below.

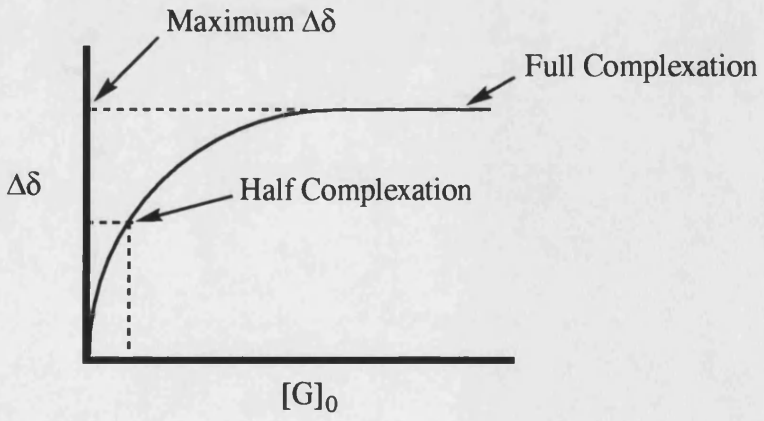
Equation 1.2:

$$K = \frac{[H\text{-}G]}{[H]\ [G]}$$

K = binding constant
[H] = equilibrium concentration of host
[G] = equilibrium concentration of guest
[H-G] = equilibrium concentration of complex

Since the values of K and [H-G] are both unknowns the equation must be simplified in order for K to be determined.

Plot 1.2:



After subjecting the experimental data to a non-linear least squares fitting procedure a plot (plot 1.2) of Δδ (change in chemical shift) against $[G]_0$ (initial concentration of guest) will

give a curve where the value of $\Delta\delta$ tends to a maximum at full complexation.[33] (This is for a titration experiment where the initial concentration of host $[H]_0$ is kept constant). At the point of half complexation, where $\Delta\delta$ is half that for full complexation, the values of [H] and [H-G] will be equal and so the expression for K simplifies to that given by equation 1.3.

Equation 1.3:

$$K = \frac{[H\text{-}G]}{[H]\ [G]}$$

If $[H] = [H\text{-}G]$ then $K = \frac{1}{[G]}$

If $[G] = [G]_0 - 1/2[H]_0$ then $K = \frac{1}{[G]_0 - 1/2[H]_0}$

$[G]_0$ = Initial guest concentration
$[H]_0$ = Initial host concentration

So from the graph the value of $[G]_0$ corresponding to half complexation can be extrapolated and hence a value for K calculated. (The value of [G] can be related to that of $[G]_0$ for half complexation by the expression $[G]=[G]_0-1/2[H]_0$). (Note that these equations only apply for half complexation). It is important to realise that a 1:1 complex of host with guest (full complexation) may not occur at the point where the initial ratio of host to guest is equal but at a larger value of $[G]_0$ relative to $[H]_0$ depending on the strength of the association. As a general rule, the steeper the gradient of the initial portion of the graph the larger will be the value of K and hence the stronger the association.

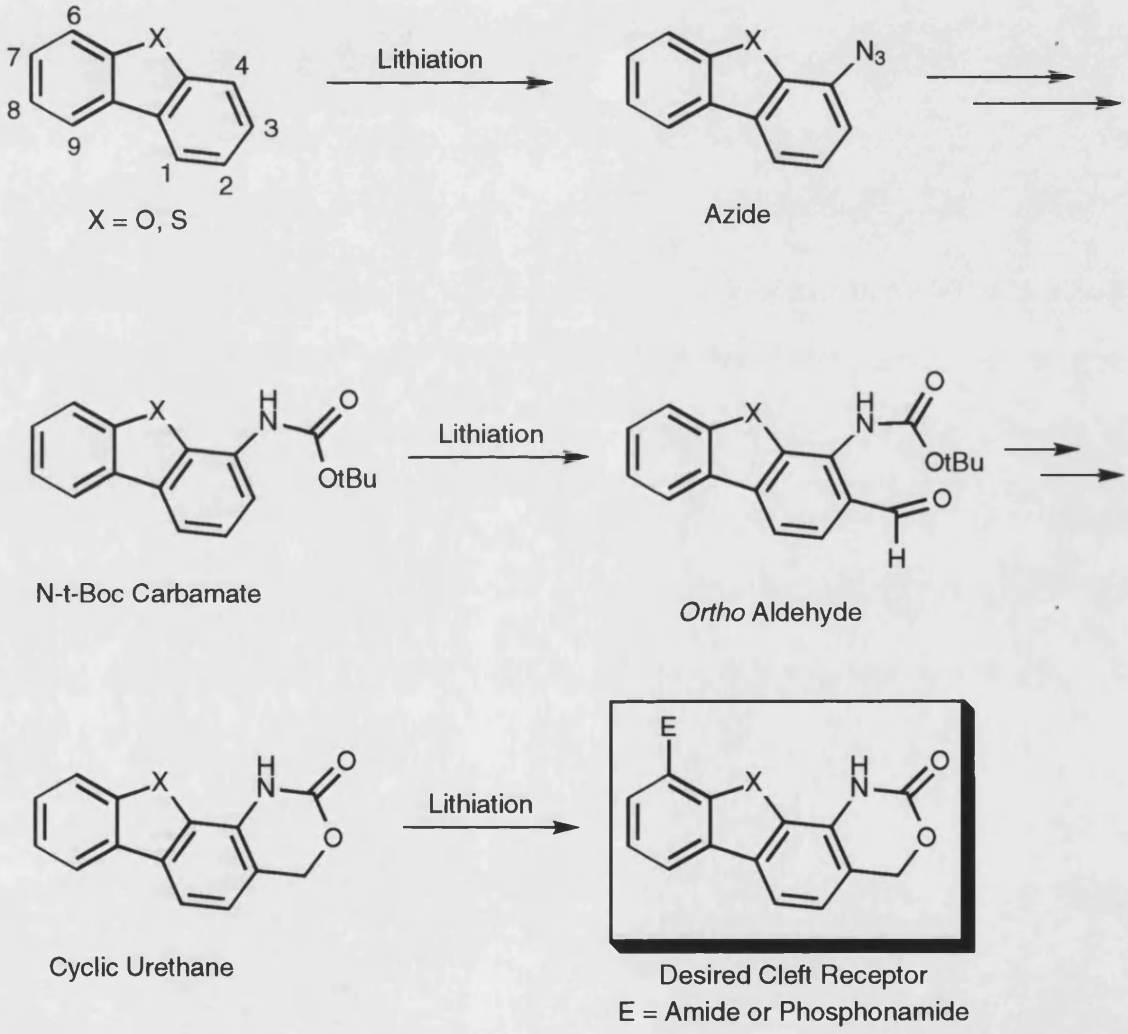
SECTION 1:

CHAPTER 2: SYNTHETIC STRATEGY

General Strategy for the Synthesis of Cleft Receptors

It was envisaged that the proposed cleft receptors could be synthesised using a sequence of *ortho* lithiation reactions as highlighted in scheme 1.1.

Scheme 1.1:



The first and third *ortho* lithiations would rely on the directing ability of the heteroatom X and the second lithiation would be directed by the N-t-Boc carbamate. This methodology would then allow for the introduction of chirality into the clefts at a late stage in the synthesis, either by incorporation of a chiral sulfoximine or a chiral phosphonamide unit. At this point it is perhaps pertinent to discuss some aspects of *ortho* lithiation.

Ortho Lithiation Reactions

The concept of directed *ortho* lithiation is clearly outlined in a review by Sniekus.[35] The directed *ortho* lithiation reaction usually comprises of the deprotonation of a site *ortho* to a heteroatom containing group (DG) using a strong base (usually an alkyllithium). Subsequent reaction of the lithiated species with an electrophile leads to a 1,2-disubstituted product (see scheme 1.2).

Scheme 1.2:

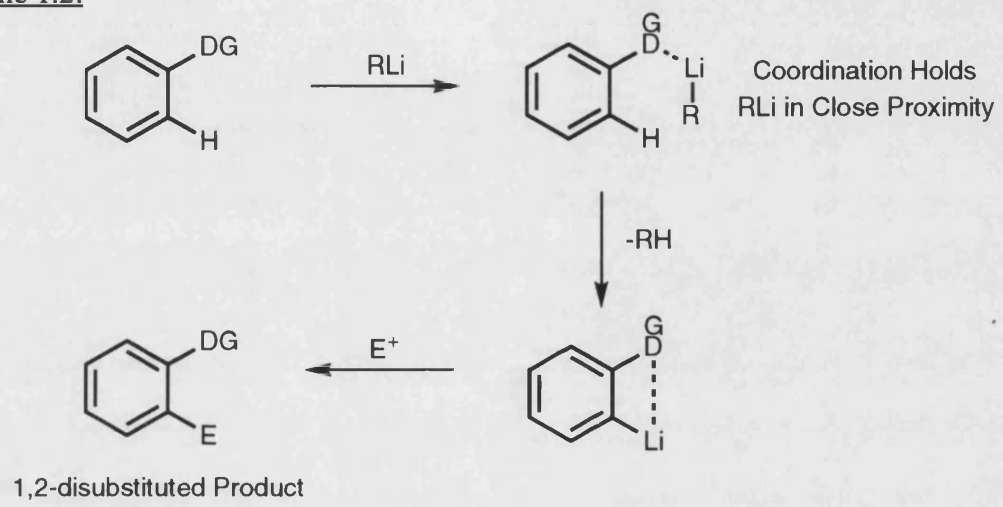
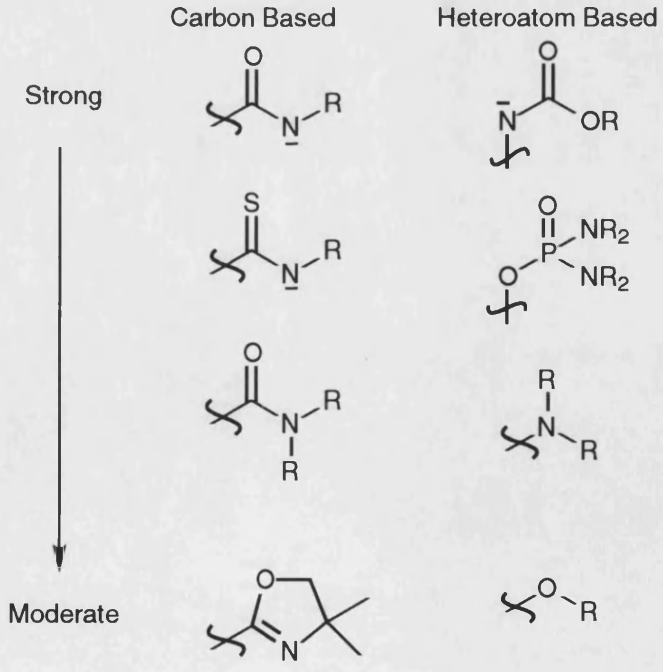


Fig. 1.14:



Ortho directing groups (DG's) work by a combination of inductive and coordinative effects. The electron withdrawing properties of the group serve to labilise the *ortho* proton via inductive effects through the σ-framework of the molecule. The coordinating properties of

the group also serve to hold the base in close proximity to the labilised *ortho* proton and thus effect deprotonation more readily.

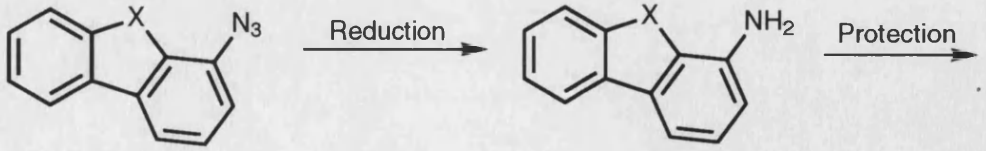
One other important property of the *ortho* directing group is that it must be a poor electrophile and should not react readily with nucleophilic alkyllithium reagents, this is usually achieved by incorporating steric hindrance or a means of charge deactivation into the directing group. Some examples of *ortho* directing groups are shown in fig. 1.14.

Lithiation of Dibenzothiophene and Dibenzofuran

The first lithiation in the sequence relies on the *ortho* directing ability of the central heteroatom (X = O, S) to generate a 4-lithiated species which can be quenched by an electrophile. In the case of dibenzothiophene lithiation at the 4-position was first achieved by Gilman and co-workers in 1958 and has since been carried out using a variety of methods.[36, 37, 38, 39] The most common method for mono lithiation of dibenzothiophene is that reported by Katritzky where treatment with two equivalents of n-BuLi in THF (important for coordinative activation of the butyllithium) at room temperature gives a good yield of 4-lithiodibenzothiophene after approximately five hours.[39] In contrast the 4-lithiation of dibenzofuran, which was also first studied by Gilman and co-workers is best achieved using one equivalent of n-BuLi in THF at room temperature.[36, 40]

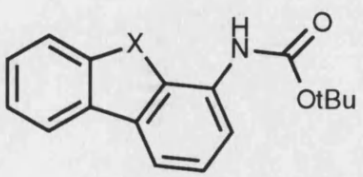
It was envisaged that the 4-lithiated species generated from either dibenzothiophene or dibenzofuran could be quenched with tosyl azide to give the 4-azido derivative which could then be reduced to the corresponding amine and protected as an N-t-Boc carbamate (see scheme 1.3).[41, 42, 43, 44] This resultant carbamate could then serve as the *ortho* directing group for the second lithiation reaction.

Scheme 1.3:



Azide

Amine

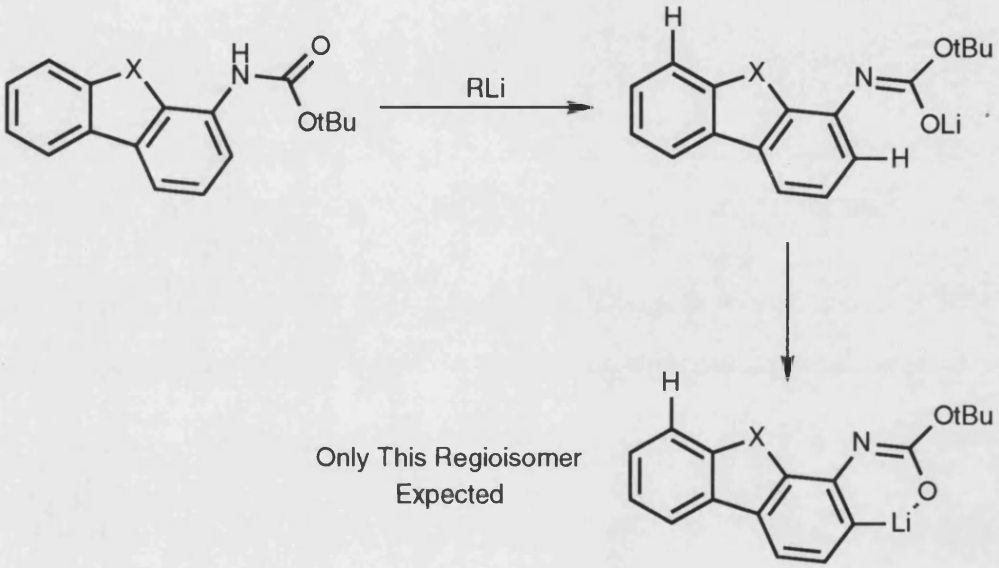


N-t-Boc Carbamate

Lithiation of the N-t-Boc Carbamate

N-t-Boc carbamate groups are well known as one of the most powerful *ortho* directing groups and it was hoped that the *ortho* directing power of this group would far outweigh any directing effect from the central heteroatom (X = O,S) thus allowing complete control over the regiochemistry of the lithiation (see scheme 1.4).[35]

Scheme 1.4:

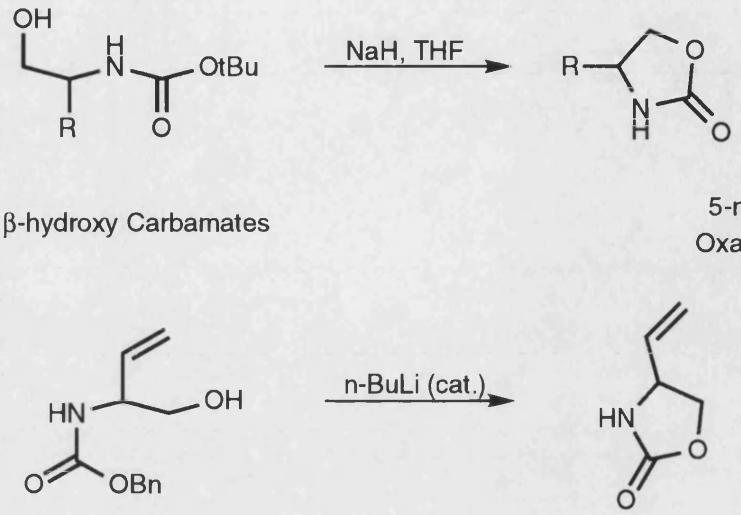


Owing to the propensity of the N-t-Boc carbamate group to react with the more nucleophilic bases such as n-BuLi the use of t-BuLi was considered to be a pre-requisite for this lithiation reaction.[45, 46] It was hoped that the *ortho* lithiated species thus generated could then be quenched by the addition of DMF to give the corresponding *ortho* aldehydes upon aqueous workup.

Formation of the Cyclic Carbamate (Urethane)

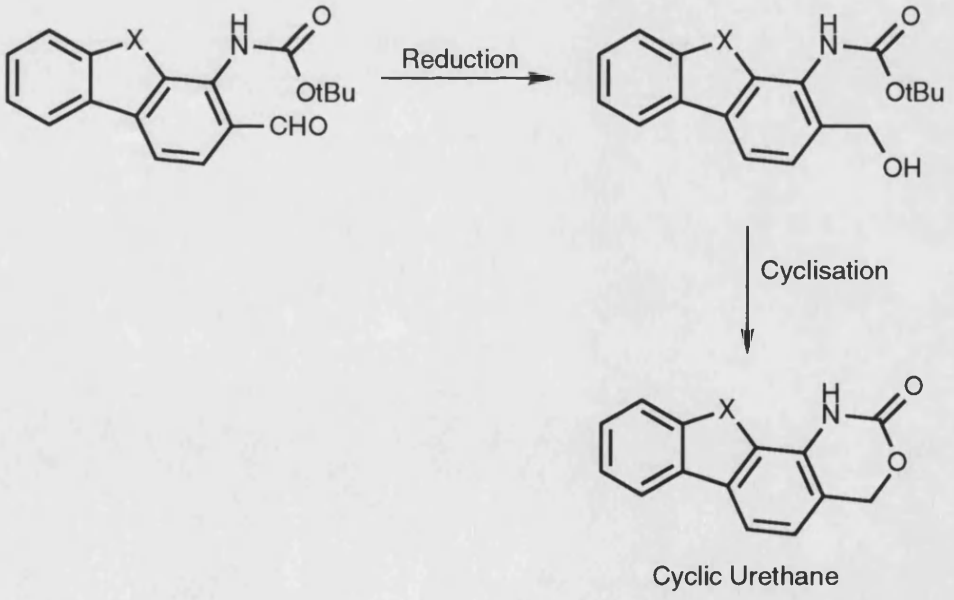
Existing literature precedents suggested that the desired cyclic urethane moiety could be generated using a base mediated ring closure of an alcohol onto the N-t-Boc carbamate group. Huwe and Blechert have reported the cyclisation of β-hydroxy carbamates to form the corresponding 5-membered oxazolidinones using sodium hydride as base.[47] A similar preparation of 5-membered oxazolidinones was also reported by Yoo and Lee but this time using n-BuLi as a catalytic base to drive the cyclisation reaction (see scheme 1.5).[48]

Scheme 1.5:



Thus it was hoped that reduction of the *ortho* aldehyde to the corresponding alcohol and treatment with base (e.g.. sodium hydride) would result in formation of the desired cyclic urethane (see scheme 1.6).

Scheme 1.6:

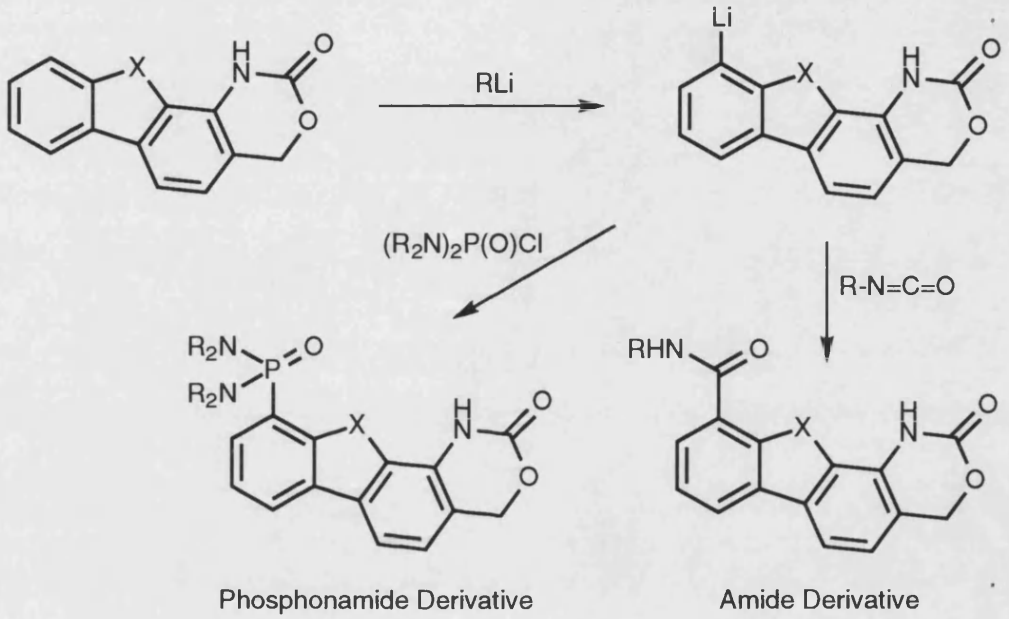


Final Lithiation Reaction

Once the cyclic urethane had been put in place it was envisaged that the final lithiation could be achieved by employing the *ortho* directing ability of X, in a similar manner to the first lithiation, to give a 6-lithiated species. At this point the synthesis could diverge to give either a *trans* amide or a phosphonamide at the 6-position (see scheme 1.7).

Due to the possible sensitivity of the sulfur (in dibenzothiophene) to oxidation it was hoped that the *trans* amide could be introduced directly without recourse to an oxidation step. Cherluck has reported the reaction of alkyl and aryllithiums with isocyanates to give *trans* amides in good yield.[49] It was hoped that this method could be employed to give a range of amides from their corresponding isocyanates, thus introducing a fair degree of versatility in receptor structure at this late stage in the synthesis.

Scheme 1.7:



Phosphonamide Derivative Amide Derivative

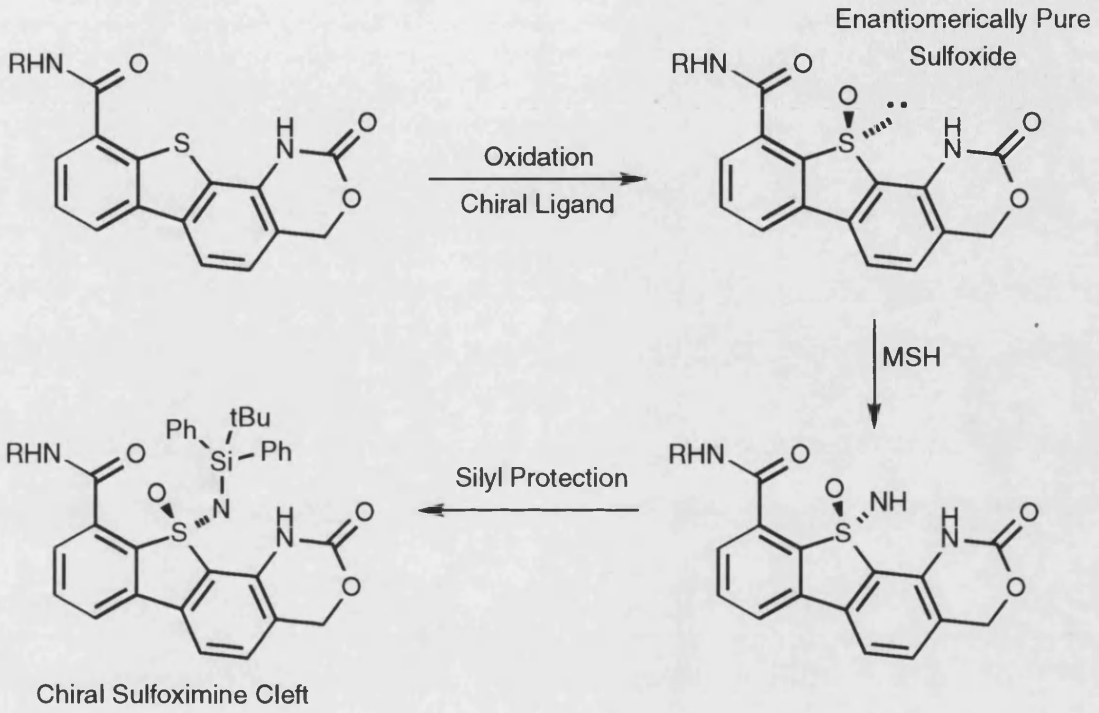
The chiral phosphonamide group could hopefully be introduced by employing the corresponding chloro phosphonamide derivatives as electrophiles in the final lithiation reaction. These chloro phosphonamide derivatives could be prepared from the parent chiral diamines as described in the General Introduction. The reaction of similar chloro phosphonamides and chloro phosphites with alkyllithiums and Grignard reagents has been demonstrated in the literature and would hopefully provide a precedent for the formation of the desired chiral phosphonamide derived receptors.[50] It was hoped that these chiral phosphonamides would exhibit enantioselective binding to amino acid N-carbamate derivatives.

Preparation of the Sulfoximine Derived Cleft Receptors

With the hydrogen bonding scaffold in place it was proposed that the dibenzothiophene derived clefts could be transformed into sulfoximines in a three step process. It was hoped that the S-oxide could be produced in enantiomerically pure form using a chiral oxidation procedure or by a resolution of the racemic sulfoxide.[51] The resultant chiral sulfoxide could then be subjected to an amination reaction using mesitylene sulfonyl hydroxylamine (MSH)

as a source of NH_2^+ which, according to work by Johnson, can be achieved with retention of stereochemistry at sulfur.[52, 53] Finally protection of the free sulfoximine with a bulky silyl group should give rise to the desired cleft receptor which would hopefully be capable of enantioselective binding to amino acid N-carbamate derivatives (see scheme 1.8).[54]

Scheme 1.8:



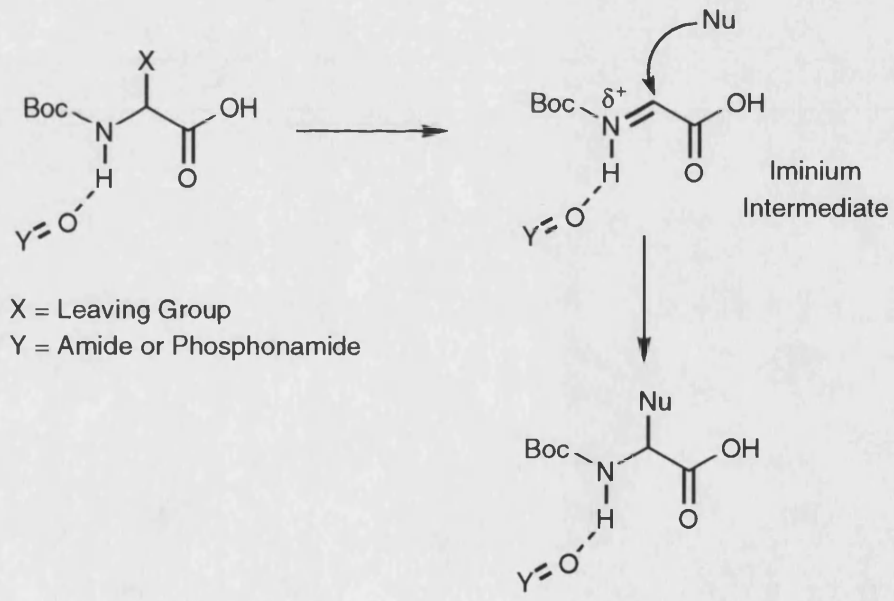
SECTION 1:

CHAPTER 3: AMINO ACID SYNTHESIS

Potential for the Proposed Cleft Receptors to Act as Catalysts for the Asymmetric Synthesis of Amino Acids

If the proposed cleft receptors were found to bind amino acid N-carbamates with a reasonable degree of enantioselectivity would it be possible to use them as catalysts for the asymmetric synthesis of amino acids? It is reasonable to suggest that binding of the C=O or P=O in the cleft to the N-H of the amino acid N-carbamate would weaken that N-H bond significantly. If the α-substituent of the amino acid N-carbamate were a good leaving group (X) then such a weakening of the N-H bond might induce X to leave giving rise to an iminium intermediate which could then be trapped by a nucleophile (see scheme 1.9). If the iminium species remained bound to the cleft, within its chiral environment, then the possibility of inducing asymmetry upon attack of the nucleophile might be realised.

Scheme 1.9:



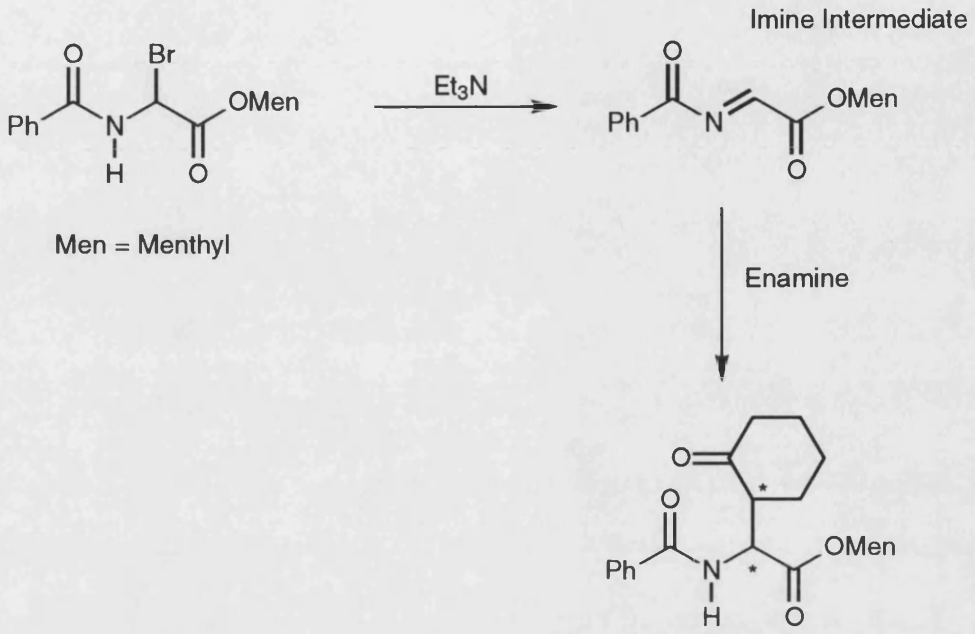
This type of substitution reaction has been demonstrated to good effect using base or Lewis acid catalysis in conjunction with chiral auxiliaries resulting in the formation of a number of enantiomerically enriched amino acids.[55]

Base Mediated Imine Formation

Steglich has studied the reaction of α-bromo glycine menthyl esters with a variety of enamines (see scheme 1.10).[56] The α-bromo glycine derivative was first treated with triethylamine to give the intermediate imine which was then reacted with an enamine to give a

novel α-substituted product with a high degree of diastereoselectivity. The selectivity of the reaction was further improved when a second auxiliary was introduced into the enamine moiety.

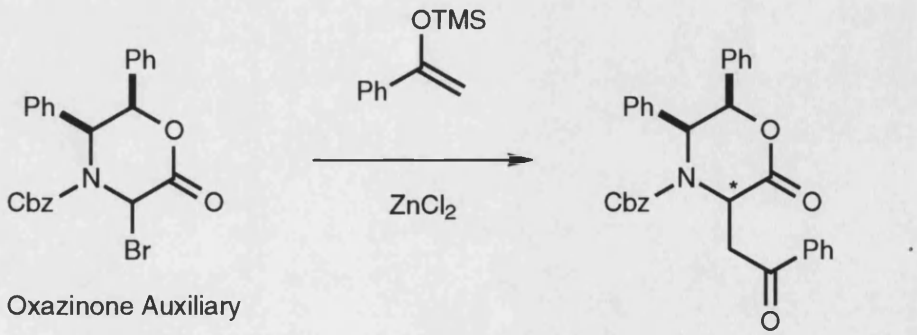
Scheme 1.10:



Lewis Acid Mediated Iminium Formation

The area of Lewis acid mediated iminium formation has been greatly explored by Williams and co-workers using a chiral oxazinone species to induce enantioselectivity (see scheme 1.11). Zinc chloride serves to induce loss of the α-bromine resulting in formation of an iminium intermediate which has been trapped with a wide variety of soft nucleophiles including; silyl enol ethers, allyl silanes and boranes and tin acetylides.[57]

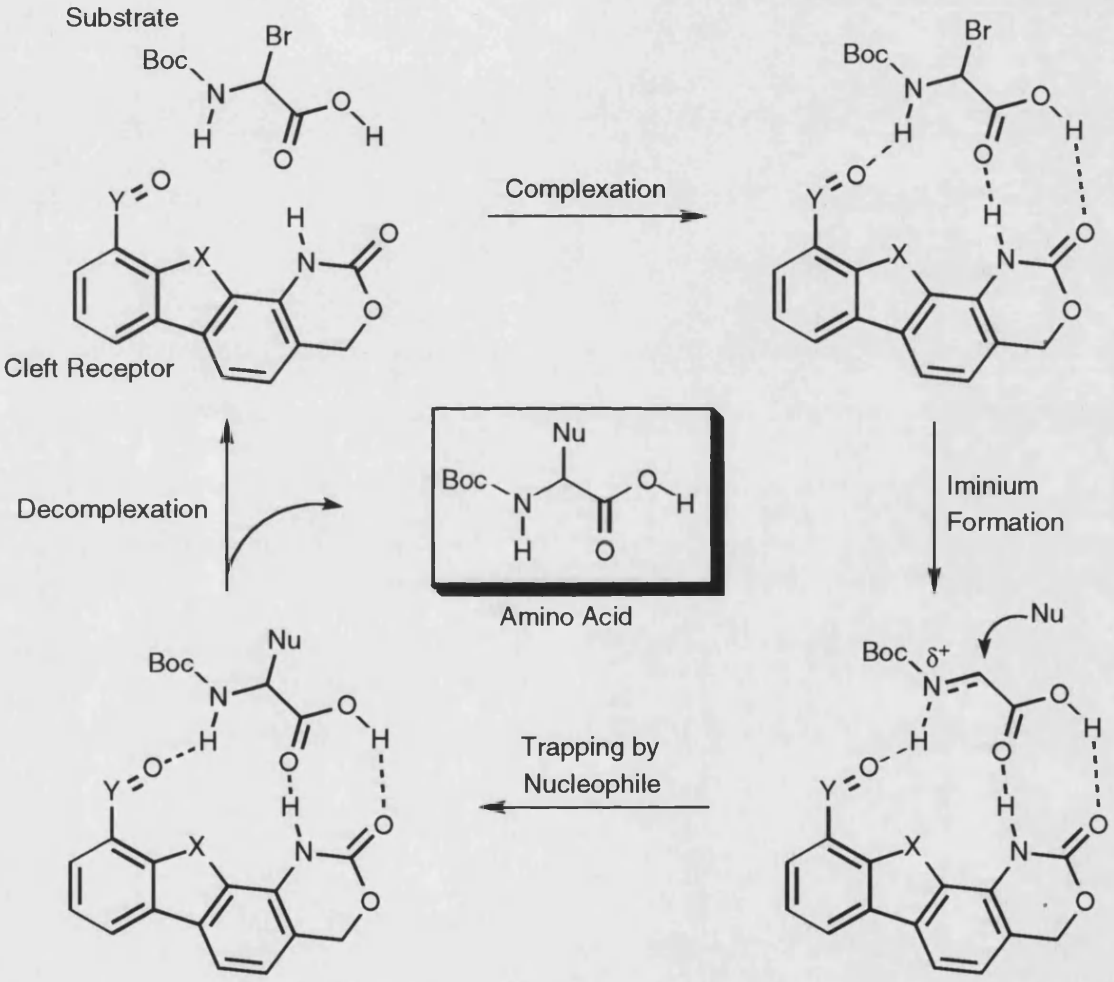
Scheme 1.11:



Asymmetric Catalysis

Whilst great success has been achieved using chiral auxiliaries for this substitution reaction no examples of asymmetric catalysis exist in the literature. It was envisaged that the cleft receptors could be used as catalysts for this reaction as shown in the proposed catalytic cycle (see scheme 1.12).

Scheme 1.12:

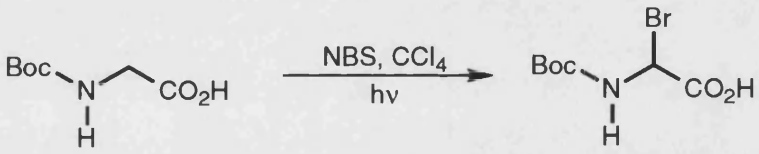


Trapping of the iminium intermediate with a soft nucleophile would give rise to an α-substituted product which would hopefully dissociate from the cleft and allow the catalytic cycle to be completed. In theory the substrate for the reaction could incorporate any suitable leaving group at the α-position (X = Halogen, OR, OAc etc.) but since most literature examples have employed bromine as the leaving group it was decided that this would be the substituent of choice in this system.

Synthesis of α-Bromo Amino Acid Derivatives

α-Bromo amino acid derivatives are usually generated by photolytic bromination of the glycine derived precursor using NBS as a bromine source.[58] It is possible to isolate the α-bromo compounds but they have been shown to be thermally unstable and thus require careful handling and storage at low temperature. It was hoped that this methodology could be applied to the synthesis of the desired N-t-Boc-α–bromo glycine which could be employed as a substrate for the proposed substitution reaction (see scheme 1.13).

Scheme 1.13:



α-Bromo Glycine Derivative

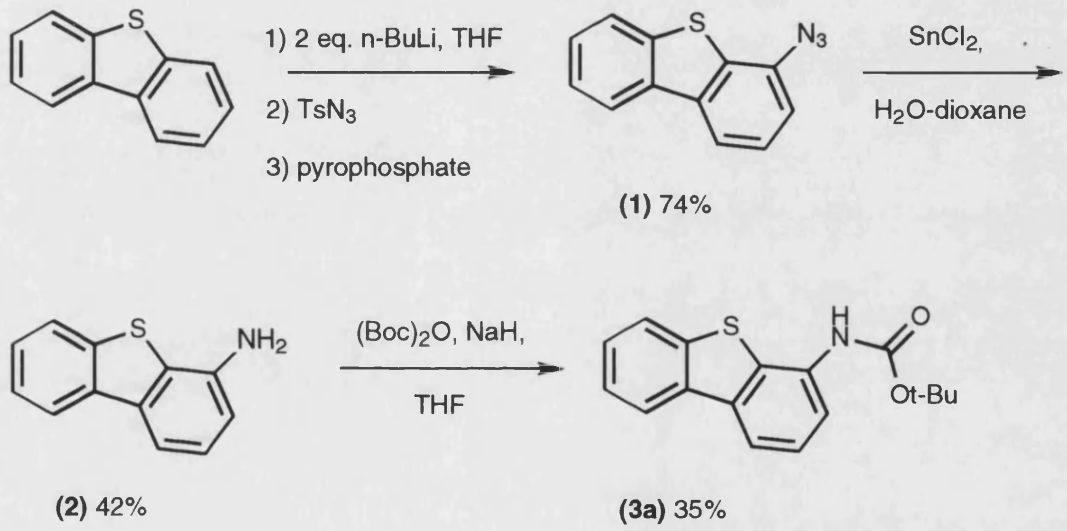
SECTION 1:

CHAPTER 4: RESULTS AND DISCUSSION

Synthetic Routes to Dibenzothiophene/Dibenzofuran-4-t-Boc-carbamate

The first key intermediate in the synthesis of the proposed cleft receptors was envisaged to be the 4-t-Boc-carbamate (**3**). Initial attempts at the preparation of (**3**) focused on the possibility of direct introduction of an azide group into the 4 position *via* a directed *ortho*-lithiation and subsequent conversion of this to the t-Boc-carbamate as outlined in scheme 1.14.

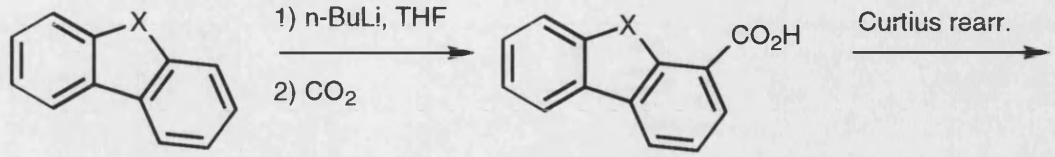
Scheme 1.14:



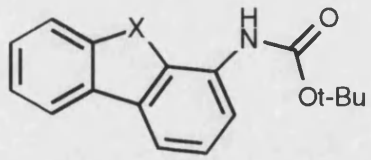
Lithiation of dibenzothiophene was achieved by using two equivalents of n-BuLi in THF, at room temperature for 5hrs.[39] It is not entirely clear why 2 equivalents of base were required to effect lithiation, but it is thought that the sulfur atom coordinates to one molecule of n-BuLi and renders it inactive, thus a second equivalent is required to perform the deprotonation. Quenching of the resultant 4-lithio-dibenzothiophene with tosyl azide[41] gave a triazene salt which was decomposed to the azide (**1**) in 74% yield by stirring with an aqueous solution of sodium pyrophosphate.[42] After purification on a Florisil® column the azide was reduced to the amine (**2**) in 42% yield,[59] using tin(II) chloride in aqueous/dioxane solution.[60] Protection of the amine proved to be very difficult under standard conditions: use of t-Boc-anhydride and triethylamine in DCM with a catalytic amount of 4-DMAP gave only 16% yield of the carbamate (**3a**). Use of refluxing methanol as solvent gave a similarly poor yield of 17%.[44, 61] Even when the amine was deprotonated with sodium hydride prior to quenching with t-Boc-anhydride only a 35% yield of carbamate was achieved. Thus a higher yielding route to the t-Boc-carbamate (**3a**) was sought.

According to literature precedent the t-Boc-carbamate could potentially be synthesised by a one pot modification of the Curtius rearrangement from the corresponding carboxylic acid (see scheme 1.15).[62, 63, 64] In order to explore this route a method for the formation of dibenzothiophene/dibenzofuran-4-carboxylic acid (**4**) was required.

Scheme 1.15:



(4a) X = S 70-80%
(4b) X = O 70-75%



(3a) X = S 70-80%
(3b) X = O 70-80%

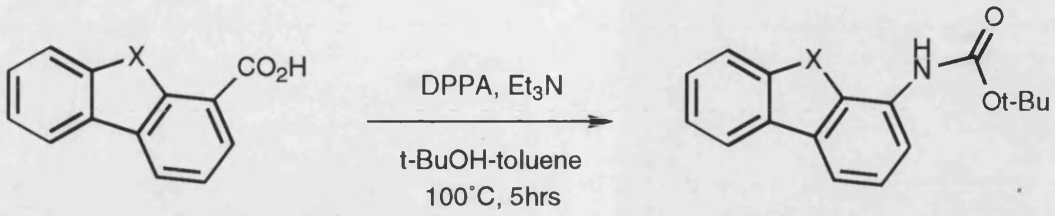
Lithiation of dibenzothiophene, using 2 equivalents of n-BuLi in THF as already described for the preparation of the 4-azide (**1**), and quenching of the 4-lithio-dibenzothiophene with solid carbon dioxide[65] gave the desired acid (**4a**) in 70-80% yield.[37] The use of solid CO_2 as opposed to CO_2 gas was very important since CO_2 gas reacts with organolithiums to give ketones, as a result of over addition due to a high relative concentration of the organolithium. Indeed in the above reaction a small amount of the corresponding ketone product was observed by t.l.c..

In the case of Dibenzofuran a similar lithiation procedure could be employed but only 1 equivalent of n-BuLi was required. Use of 2 equivalents of n-BuLi resulted in complete bis-lithiation and gave only the diacid product. Quenching of the 4-lithio-dibenzofuran with solid CO_2 gave the acid (**4b**) in 70-75% yield.[36]

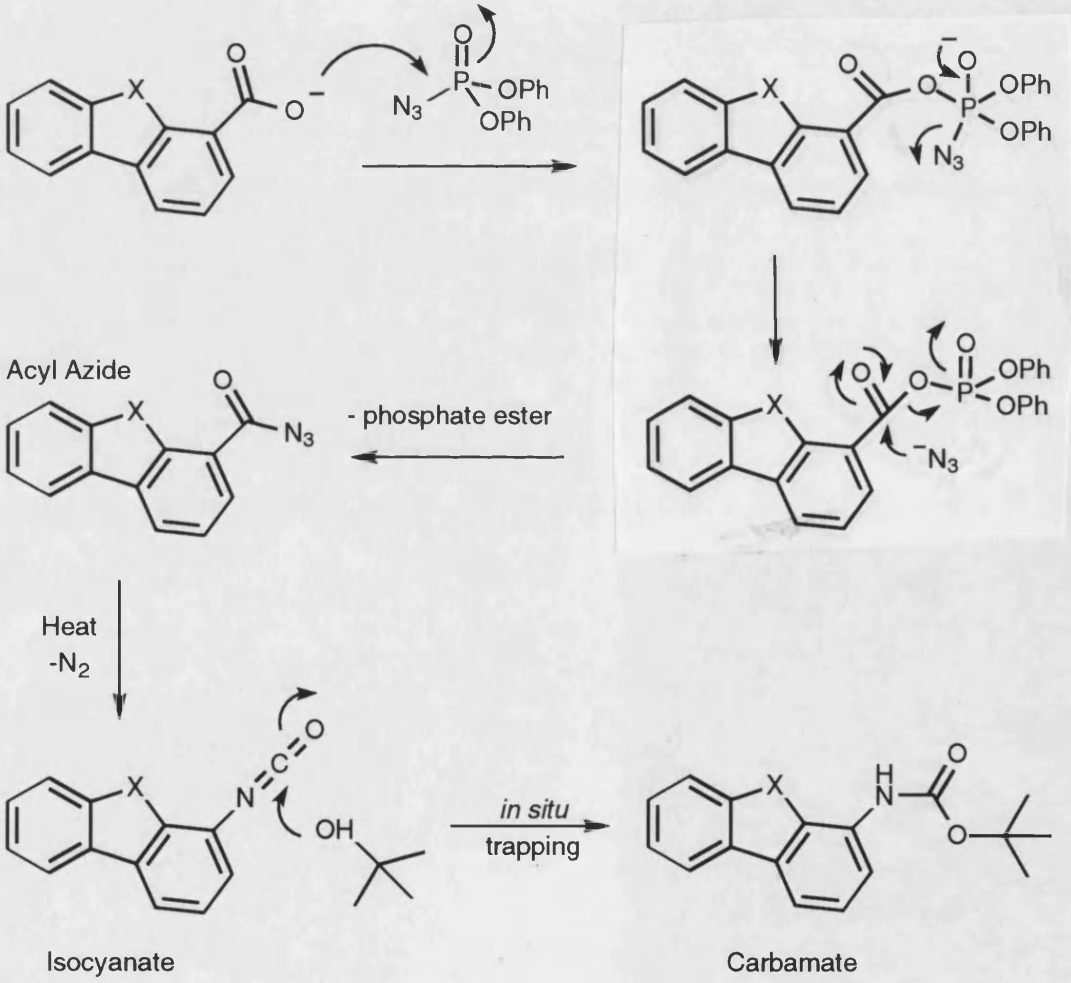
With the desired acids (**4**) in hand the modified Curtius rearrangement could be investigated. Rapid reaction of the acid with 5 equivalents of diphenyl phosphoryl azide (DPPA) under basic conditions (5 equivalents of triethylamine) in a 1:1 toluene/t-BuOH mixture gave the intermediate acyl azide, which rearranged to an isocyanate upon heating to reflux. The isocyanate was trapped *in situ* by the t-BuOH to give the t-Boc-carbamate (**3**) directly (see scheme 1.16). Excess DPPA could be reduced to the polar phosphoramide using a tin(II) chloride aqueous/THF procedure during work-up to aid purification of the product. After some experimentation with conditions it was found that meticulous drying of solvents and

purification of all starting materials enabled isolation of the carbamates (**3**), as crystalline solids, in reproducible yields of 75-80% in both cases. (Any water present reacted with the intermediate isocyanate to give a carbamic acid which decomposed to the unprotected amine upon workup).

Scheme 1.16:



Mechanism:



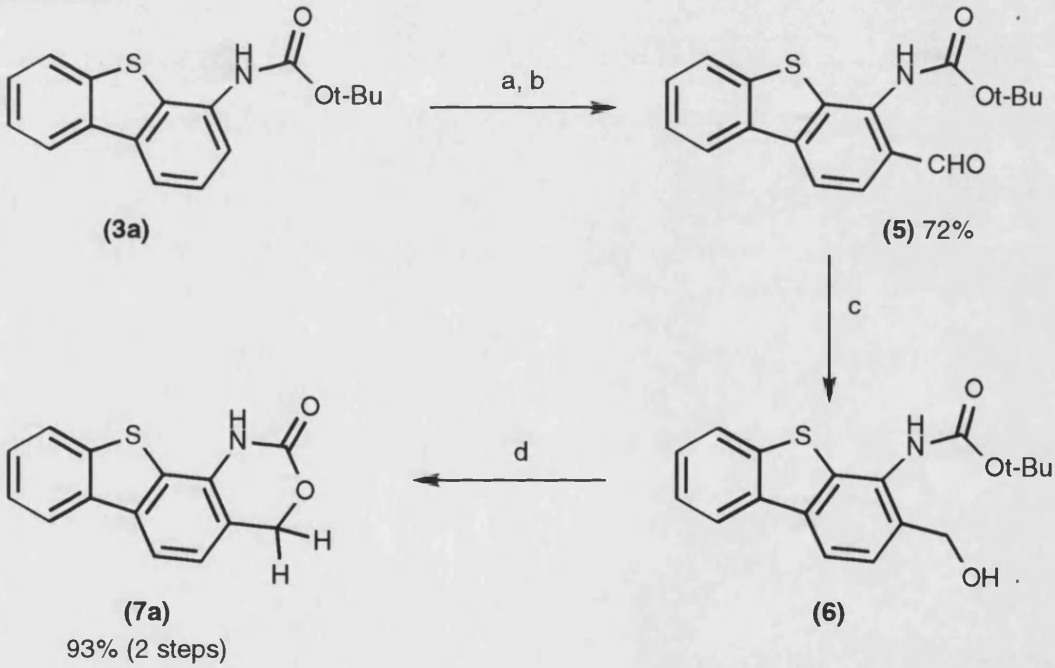
Formation of the Cyclic Urethane Intermediates

Initial studies concentrated on the derivatisation of dibenzothiophene-4-t-Boc-carbamate (**3a**). Lithiation of the carbamate was achieved using a modification of the procedure

recommended by Stanetty.[46] As discussed in the introduction the use of t-BuLi as base for the lithiation of t-Boc-carbamates is preferred. Owing to the powerful reactivity of this base the use of THF as solvent is not recommended and thus ether was used as an alternative. After some experimentation it was discovered that lithiation did not occur at temperatures below 0°C but stirring at this temperature for 2hrs gave the *bis* anion in essentially quantitative yield. This could then be quenched by a variety of electrophiles.

Since the simplest conceivable urethane was that derived from 3-methyl alcohol (**6**), DMF was used as the electrophile in the lithiation step to give the aldehyde (**5**) in 72% yield. Reduction of this aldehyde using sodium borohydride and cyclisation of the intermediate alcohol (**6**), using 2 equivalents of sodium hydride in ether at room temperature, gave the urethane (**7a**) in 93% yield (see scheme 1.17).[47, 48] Unfortunately this urethane exhibited very poor solubility in most solvents, thus more soluble analogues were sought.

Scheme 1.17:

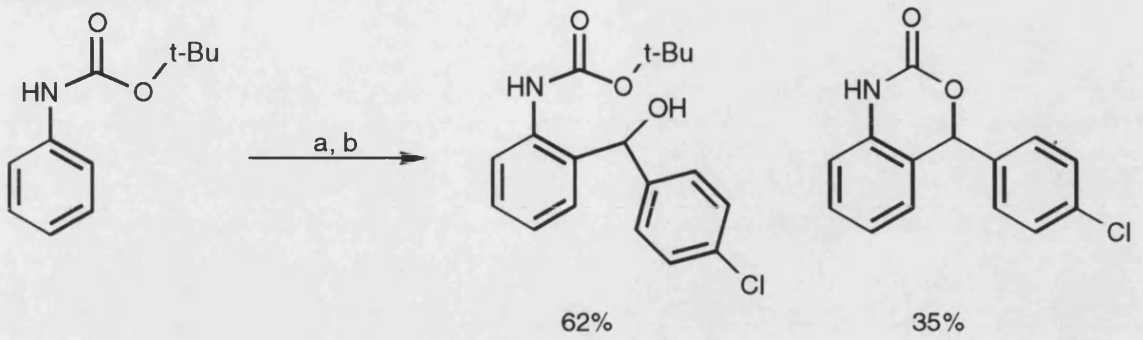


a) 2.5eq t-BuLi, Et_2O, -78-0°C, 2hrs; b) DMF, -78-20°C; c) $NaBH_4$, MeOH;
d) NaH, Et_2O.

The use of symmetrical ketones as electrophiles in the lithiation reaction was expected to give rise to alcohol intermediates which could then be cyclised to give urethanes using sodium hydride as described above. It was hoped that urethanes of this type would show improved solubility due to an increase in lipophilicity adjacent to the highly polar urethane unit. This type of reaction, using ketones and aldehydes as electrophiles, had been reported by Muchowski and Venuti.[45] In their example (see scheme 1.18), the major product observed was the alcohol and only a small amount of cyclic urethane was isolated when overnight

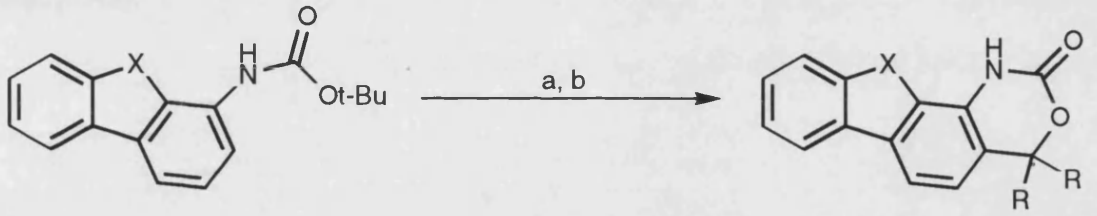
stirring at room temperature was allowed. In the case of (**7b-d**) complete cyclisation to give urethanes was observed when analogous reaction conditions were employed (see scheme 1.19 and table 1.1).

Scheme 1.18:



a) 2.4 eq t-BuLi, -20°C 2hrs; b) p-chloro benzaldehyde, -20°C 2hrs, rt. 16hrs

Scheme 1.19:



(3) (7)

a) 2.5eq t-BuLi, Et_2O, -78-0°C, 2hrs; b) R_2CO, Et_2O, -78-20°C.

Table 1.1:

Compound	X	Electrophile	R	Yield (%)
7b	S	Me_2CO	Me	40-60
7c	S	Ph_2CO	Ph	97
7d	S	$(p\text{-Tol})_2CO$	p-Tol	75
7e	O	Ph_2CO	Ph	79

These unexpected results thus enabled the synthesis of the cyclic urethanes (**7b-d**) *via* a high yielding one-pot procedure. The reaction using acetone as electrophile gave an intermediate alcohol which was observed to cyclise more rapidly than the corresponding benzophenone adduct, probably due to a significant difference in steric hindrance. However, the reaction with acetone proved to be unreproducible with variable amounts of self-aldol condensation side products being formed. The use of non-enolisable ketones such as benzophenone and 4,4'dimethyl benzophenone was thus preferred.

When this lithiation-cyclisation methodology was applied to the dibenzofuran-4-N-t-Boc-carbamate (**3b**) a rather disappointing result was obtained. Only a 62% yield of the desired urethane (**7e**) could be achieved after stirring at room temperature for 4 days! It appeared that, in this case, the cyclisation reaction was very much slower. Interestingly the remaining uncyclised alcohol (**7f**), isolated from this reaction, could be cyclised rapidly to the urethane using the previously described method with 2 equivalents of sodium hydride, giving (**7e**) in an overall yield of 79%. Clearly the nature of the cation affected the rate of the cyclisation quite dramatically. The sodium cation being harder and less coordinating enabled the formation of a "naked" anion which was then able to participate in the cyclisation reaction more effectively. This does not, however, explain the dramatic difference in reactivity between the dibenzofuran and dibenzothiophene systems and for this a consideration of possible mechanisms of cyclisation was required.

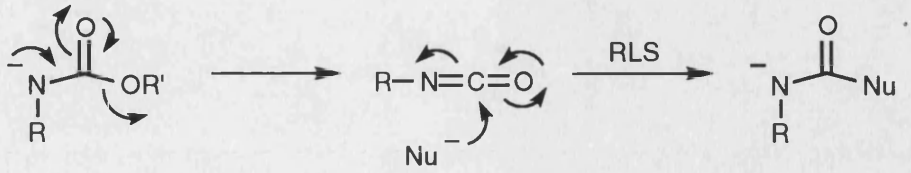
According to literature there are three possible mechanisms by which a carbamate can react with a nucleophile (see scheme 1.20).[66] The first is an E_1CB mechanism whereby loss of an alkoxide produces an intermediate isocyanate which reacts with a nucleophile in a rate limiting step (RLS). The second is reaction of the nucleophile to give a tetrahedral intermediate which collapses with expulsion of an alkoxide in a rate limiting step. The final possibility is a less precedented direct displacement of alkoxide by the nucleophile without formation of a tetrahedral intermediate.

Kinetics studies have shown that the prevailing mechanism depends on a variety of factors.[67] Firstly the nature of the leaving alkoxide is important. If the alkoxide is a good leaving group, i.e. it can effectively stabilise a negative charge, then the E_1CB mechanism is favourable. This process has been demonstrated only with aryl alkoxides and is unlikely to be the favoured mechanism in this case. In cases where there is a choice between E_1CB and the alternative addition-displacement mechanism then the nature of the nucleophile is important. Oxygen nucleophiles favour addition-displacement whereas nitrogen nucleophiles favour E_1CB. The nature of the nitrogen substituent (R), in the carbamate, is thought to have little effect in determining which pathway prevails.

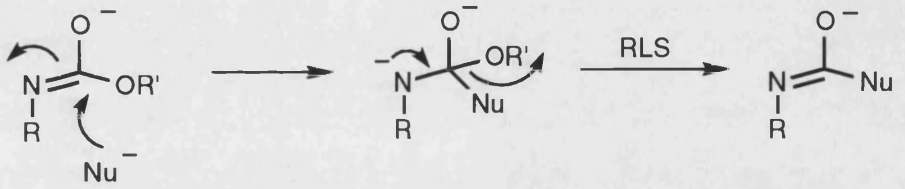
Considering the above information, it is likely that the cyclisation to urethanes (**7**) proceeds *via* formation of a tetrahedral intermediate which collapses to product in the rate limiting step. It is the ability of the respective tetrahedral intermediates to collapse to products which holds the key to the difference in reactivity observed for the dibenzofuran and dibenzothiophene systems.

Scheme 1.20:

E_1CB Mechanism:



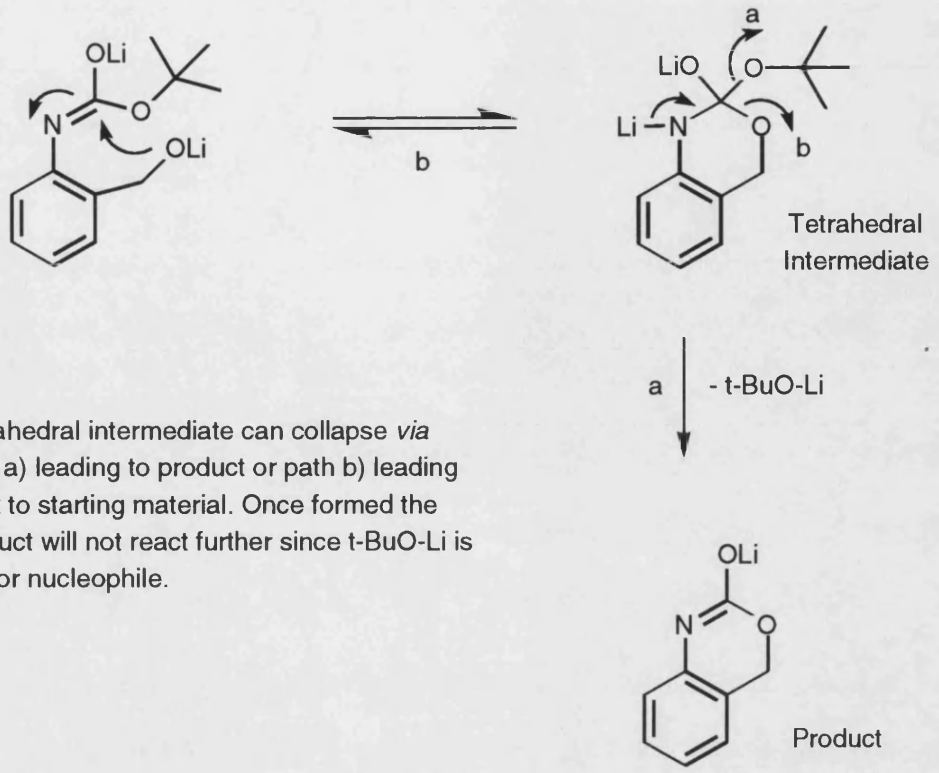
Addition-Displacement Mechanism:



Direct Displacement Mechanism:

The heterocyclic oxygen and sulfur atoms are known to possess very different lone-pair geometries. The sulfur lone pairs in dibenzothiophene are sp^3 hybridised. Evidence for this derives from molecular orbital calculations[38] and from X-ray analysis of a dibenzothiophen-4-(diphenyl)-phosphine ruthenium complex in which the ruthenium atom is clearly coordinated to sulfur in a tetrahedral geometry.[68] Conversely the oxygen lone pairs in dibenzofuran are sp^2 hybridised; one is able to delocalise into the aromatic system *via* a *p* orbital and the other lies parallel to the aromatic plane in an sp^2 orbital. Evidence for this is derived from ^{17}O NMR studies of dibenzofuran systems.[40]

Scheme 1.21:

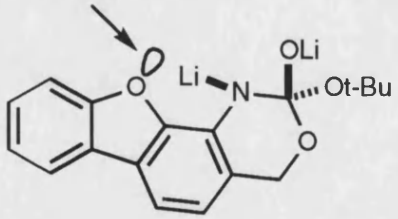


Tetrahedral intermediate can collapse *via* path a) leading to product or path b) leading back to starting material. Once formed the product will not react further since t-BuO-Li is a poor nucleophile.

Scheme 1.22:

Dibenzofuran: Oxygen is sp^2 Hybridised.

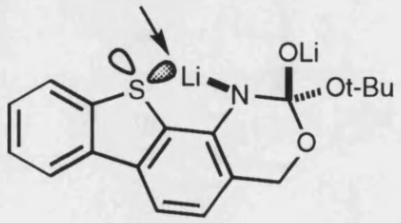
Lone pair geometry wrong for overlap with Li



No assisted breakdown of the tetrahedral intermediate can occur.

Dibenzothiophene: Sulfur is sp^3 Hybridised.

Lone pair geometry good for overlap with Li



Sulfur-Li interaction assists breakdown of the tetrahedral intermediate.

It seems possible that breakdown of the tetrahedral intermediate would be assisted by coordination of the ring heteroatom to the lithium on the carbamate nitrogen resulting in a weakening of the lithium-nitrogen bond (see scheme 1.21). Given the differing geometries of the oxygen and sulfur lone pairs it is likely that the sulfur could participate in an interaction with the tetrahedrally disposed lithium atom, (the carbamate nitrogen is sp^3 hybridised in the tetrahedral intermediate), whereas oxygen could not (see scheme 1.22). This would not only explain the enhanced reactivity of dibenzothiophene derived systems in the cyclisation reaction, but also the reason why cyclisation was observed to be slow in Muchowski and Venuti's case where no heteroatom was available for such a coordination (see scheme 1.18). Also the reason for enhanced reactivity when sodium hydride was employed is much clearer, since the interaction between sodium and the carbamate nitrogen is much more ionic in nature, the tetrahedral intermediate would collapse much more readily in both the dibenzothiophene and dibenzofuran examples.

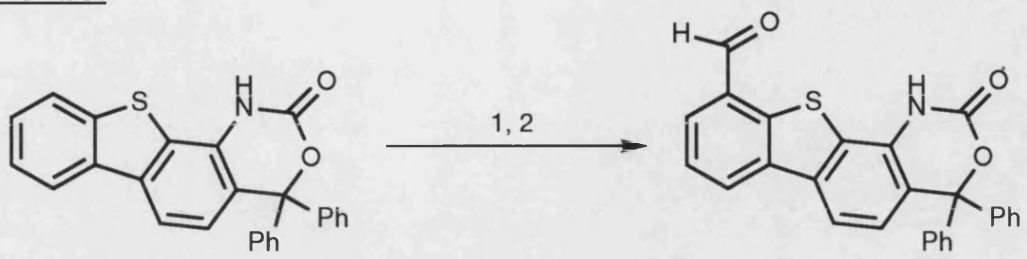
Final Lithiation Step: Formation of Potential Cleft Receptors

Lithiation of the cyclic urethane (**7c**) at the 6-position, *ortho* to sulfur, proved to be very problematic. Use of n-BuLi in THF resulted in the formation of a complex mixture of products thought to be the result of direct attack by n-BuLi on the urethane moiety. This type of nucleophilic displacement had been reported by Stannety in his study of N-t-Boc-carbamate lithiations.[46] In order to avoid such problems of nucleophilic attack the lithiation was attempted using a more hindered base. Use of t-BuLi resulted in decomposition and no product could be isolated; although t-BuLi is hindered it is also a very powerful base and prone to side reactions particularly with ethereal solvents.

According to a study by Cram and co-workers the bis lithiation of dibenzofurans can be achieved by use of s-BuLi-TMEDA.[69] This combination is considered to be non-nucleophilic and can be used in ether rather than THF because of the coordinative activation afforded by the TMEDA. The possibility of using ether as solvent also meant that the lithiation could be carried out at room temperature (alkyl lithiums have a longer half life in ether compared to THF at room temperature[46]). Application of the s-BuLi-TMEDA system in this lithiation reaction, after considerable experimentation with conditions, gave a good degree of the desired 6-lithiated urethane. The best conditions were found to be 3 equivalents of 1:1 s-BuLi-TMEDA in ether, stirring at room temperature for 3 hours. Interestingly the use of less than 3 equivalents of base gave no lithiation. Presumably the first equivalent of base was required for removal of the urethane N-H, the second coordinated to the heterocyclic sulfur (cf. the lithiation of dibenzothiophene), and thus the third equivalent performed the desired deprotonation.

Quenching of the 6-lithiated urethane species with DMF as electrophile gave aldehyde (**8a**) in 54% yield, the remaining material being recovered starting material which could be recovered and recycled (see scheme 1.23).

Scheme 1.23:

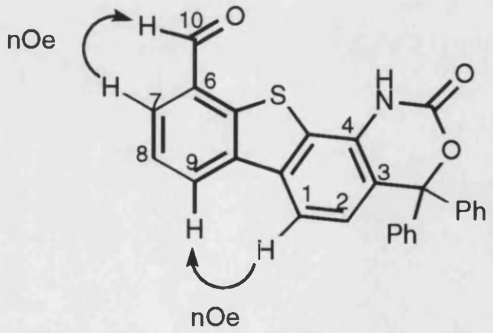


(**8a**) 54%

1) 3eq s-BuLi-TMEDA, ether, -78-20°C, 3hrs; 2) DMF, ether.

A report by Haenel and co-workers highlighted the possibility of forming 9-substituted products in a similar lithiation of dibenzothiophene using refluxing ether as solvent. Under such forcing conditions it was clearly possible for lithio-migration from the 6 to the 9-position to occur.[70] It was therefore considered important to determine the regiochemical outcome of the dibenzothiophene diphenyl urethane lithiation in order to verify that the desired 6 rather than 9-lithiation had occurred. The regiochemistry of (**8a**) was verified using a combination of COSY and NOESY NMR techniques. Careful analysis of the COSY spectrum enabled a full assignment of all the signals to individual protons present in (**8a**). Subsequently the NOESY data obtained clearly demonstrated that the 6-substituted product (**8a**) was the exclusive product of this lithiation reaction; showing an nOe between ring protons 1 and 9 and between aldehyde proton 10 and ring proton 7 (see fig. 1.15). (Copies of the COSY and NOESY spectra are included in Appendix Chapter 2).

Fig. 1.15:



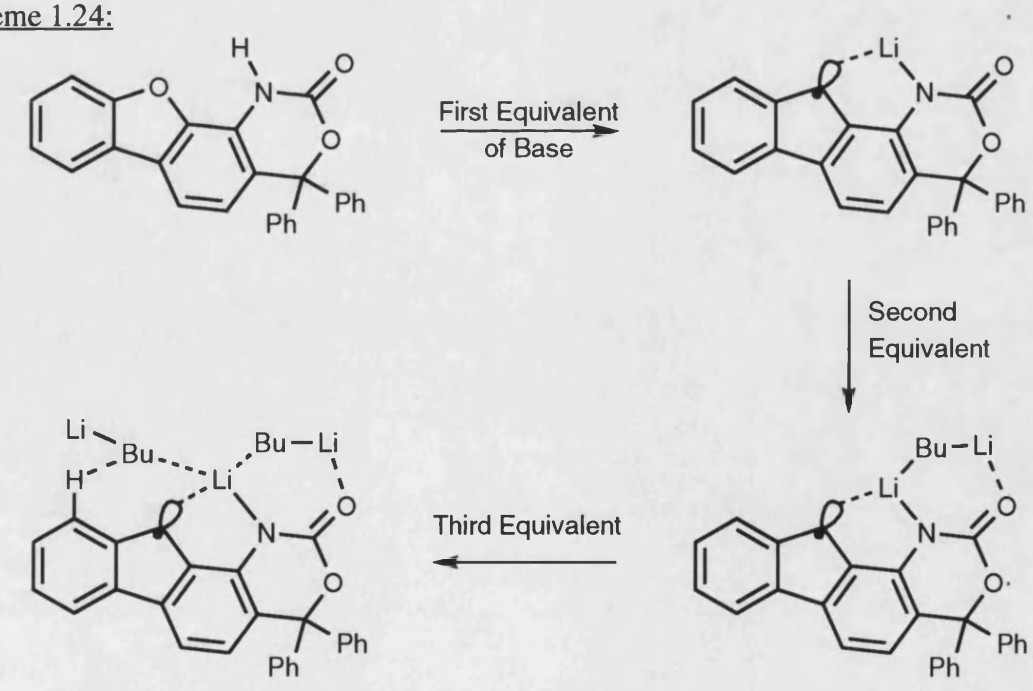
nOes were clearly observed between protons 1-9 and 7-10.

Once optimised this final lithiation procedure could be applied to a variety of electrophiles. Since the proposed dibenzothiophene derived hosts required an amide functionality at the 6-position a direct route to these compounds was sought. Some precedent for the use of

isocyanates as electrophiles in lithiation reactions had been demonstrated in the literature and their use was envisaged to enable direct access to the desired amides in one step without the need for an oxidation procedure.[49] (This was considered very important due to the oxidation sensitivity of the heterocyclic sulfur atom). Reaction of urethane (**7c**) with phenyl isocyanate under the described conditions gave phenyl amide (**8b**) in an acceptable 50% yield. Use of benzyl isocyanate yielded 52% of the desired benzylamide (**8c**). Both of the amides where highly crystalline materials which aided purification.

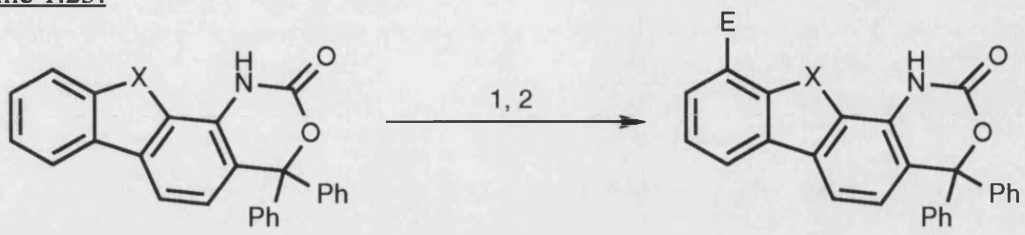
The proposed diazaphospholidine oxide cleft receptors could in principle be derived form either the dibenzothiophene urethane (**7c**) or the dibenzofuran urethane (**7e**). Lithiation of urethane (**7e**) using the same conditions as for (**7c**) gave a good degree of lithiation at the 6-position. It was however a little surprising that 3 equivalents of base were still required in order to effect lithiation instead of the expected 2 equivalents. This was clearly contrary to the case for dibenzofuran lithiation where only one equivalent of base was required compared to the 2 required by dibenzothiophene. A possible explanation for this lies again with the lone pair orbital geometry of the heterocyclic oxygen atom. After initial removal of the carbamate N-H, coordination of the nitrogen bound lithium atom to the heterocyclic oxygen to form a 5 membered, planar chelate would probably occur. This chelate could then coordinate to a second molecule of alkyllithium and render it inactive towards deprotonation and thus a third equivalent of base would be required in order to effect the desired deprotonation (see scheme 1.24).

Scheme 1.24:



In order to test the applicability of phosphorus based electrophiles in this final lithiation both (**7c**) and (**7e**) were lithiated and reacted with diphenyl phosphoryl chloride to give the corresponding phosphine oxides (**8d**) and (**8e**) in 56 and 49% yield respectively (see scheme 1.25 and table 1.2). This encouraging result demonstrated the potential of using this method to form the desired diazaphospholidine oxide derived cleft receptors.

Scheme 1.25:



(**8**)

1) 3eq s-BuLi-TMEDA, ether, -78-20°C, 3hrs; 2) E^+, ether.

Table 1.2:

Compound	X	E^+	E	Yield (%)
8a	S	DMF	CHO	54
8b	S	PhNCO	CONHPh	50
8c	S	BnNCO	CONHBn	52
8d	S	$Ph_2P(O)Cl$	$P(O)Ph_2$	56
8e	O	$Ph_2P(O)Cl$	$P(O)Ph_2$	49

Derivatisation of Dibenzothiophene Compounds at Sulfur.

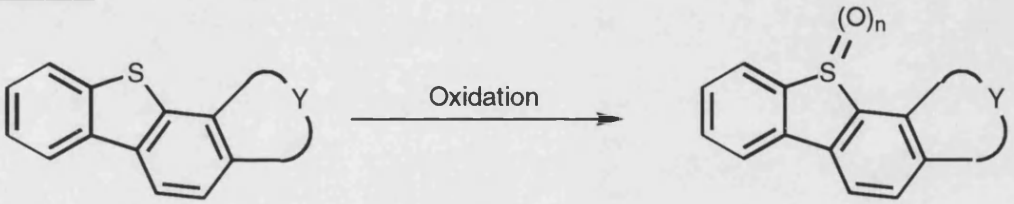
Initial attempts to derivatise the dibenzothiophene derived clefts at sulfur focused on synthesis of racemic compounds. It was decided that only once a method for the formation of the proposed sulfoximine clefts had been elucidated would a route to optically pure sulfoximines, *via* the corresponding sulfoxides, be investigated.

Oxidation of dibenzothiophene to the sulfoxide (**9**)[71] could be best achieved by using electrophilic oxidation systems to minimise over oxidation to the sulfone (**10**) (electrophilic oxidants are expected to react favourably with electron rich sulfides but less so with the more electron deficient sulfoxides).[72] Whilst acidic peroxide (t-BuOOH, $HClO_4$), considered to be a highly electrophilic oxidant, did give only sulfoxide (**9**) the yield was poor (19%). *m*CPBA, which is an electrophilic oxidant but closer to the border line between electro- and nucleophilicity than acidic peroxide, proved to be a better oxidant. This gave a mixture of sulfoxide (**9**) 62% and sulfone (**10**) 26%, after stirring at room temperature overnight,

which could be readily separated by column chromatography. If the reaction was quenched after 1 hour only a trace of sulfone (**10**) was observed and the sulfoxide (**9**) could be isolated in a respectable 52% yield, the remaining starting material could also be recovered and recycled in this reaction.

With a suitable protocol in hand the oxidation of dibenzothiophene derivative (**7c**) was attempted. *m*CPBA oxidation of (**7c**) gave the sulfoxide (**11**) in a 62% yield after 1 hour at room temperature (see scheme 1.26 and table 1.3). Again the remaining starting material could be recovered and recycled.

Scheme 1.26:



n = 1 (**9**)
n = 2 (**10**)
n = 1, Y = urethane (**11**)

Table 1.3:

Compound	Oxidant	Conditions	Yield n=1 (%)	Yield n=2 (%)
DBT	t-BuOOH/H^+	rt.	19 (**9**)	-
DBT	*m*CPBA	rt. 16hrs	62 (**9**)	26 (**10**)
DBT	*m*CPBA	rt. 1hr	52 (**9**)	trace
7c	*m*CPBA	rt. 1hr	62 (**11**)	trace

(DBT is an abbreviation for dibenzothiophene).

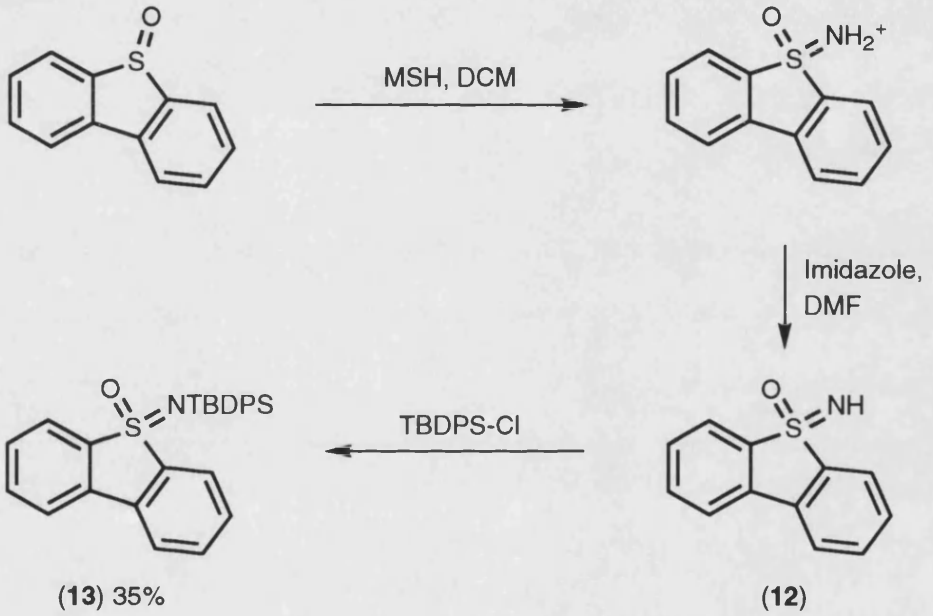
Having demonstrated that the key intermediate (**7c**) could be oxidised to give sulfoxide (**11**) the next target was to establish a protocol for the synthesis of the corresponding sulfoximine compound. According to the method of Tamura and Johnson, as discussed in Section 1 Chapter 2, a free sulfoximine could be synthesised directly from the corresponding sulfoxide using mesitylene sulfonyl hydroxylamine (MSH) as a source of NH_2^+.[52, 53]

Treatment of sulfoxide (**9**) with MSH in DCM at room temperature for 6 days gave the sulfoximine salt. Reaction of this salt with aqueous hydroxide or sodium methoxide (as described by Johnson and Tamura respectively), did not give any of the expected free sulfoximine (**12**). It appeared that any slight excess of either of these nucleophilic bases served to reverse the amination reaction and gave only starting sulfoxide (**9**) upon workup. However some free sulfoximine (**12**) was isolated when the non-nucleophilic base imidazole was used. Since imidazole was also the base required for the silylation reaction to give the

desired TBDPS-sulfoximine (**13**), a one-pot synthesis of this compound was attempted. Reaction of sulfoxide (9) with MSH, as before, gave a suspension of sulfoximine salt which, after 6 days at room temperature, was evaporated to dryness and redissolved in DMF along with imidazole followed by TBDPS-Cl. After 16 hours at room temperature the silyl sulfoximine (**13**) was isolated in 35% yield (see scheme 1.27).

Unfortunately all attempts to derivatise sulfoxide (**11**) as the silyl sulfoximine failed and thus it was decided that attention should be focused on the more promising area of diazaphospholidine oxide derived cleft receptors.

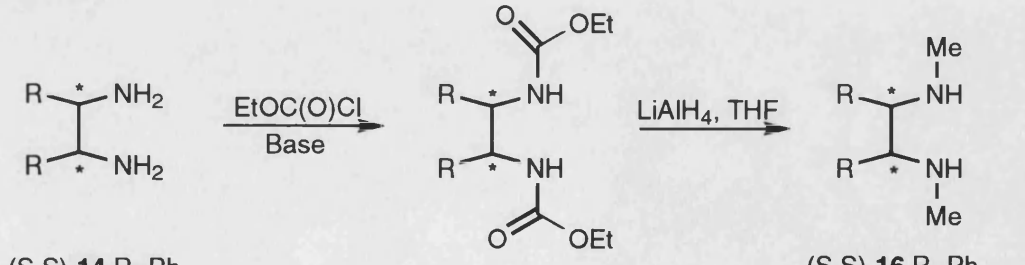
Scheme 1.27:



(**13**) 35% (**12**)

Diazaphospholidine Oxides Derived from Chiral C_2-symmetric Diamines

Scheme 1.28:



(S,S)-**14** R=Ph
(R,R)-**15** R=-C_4H_8

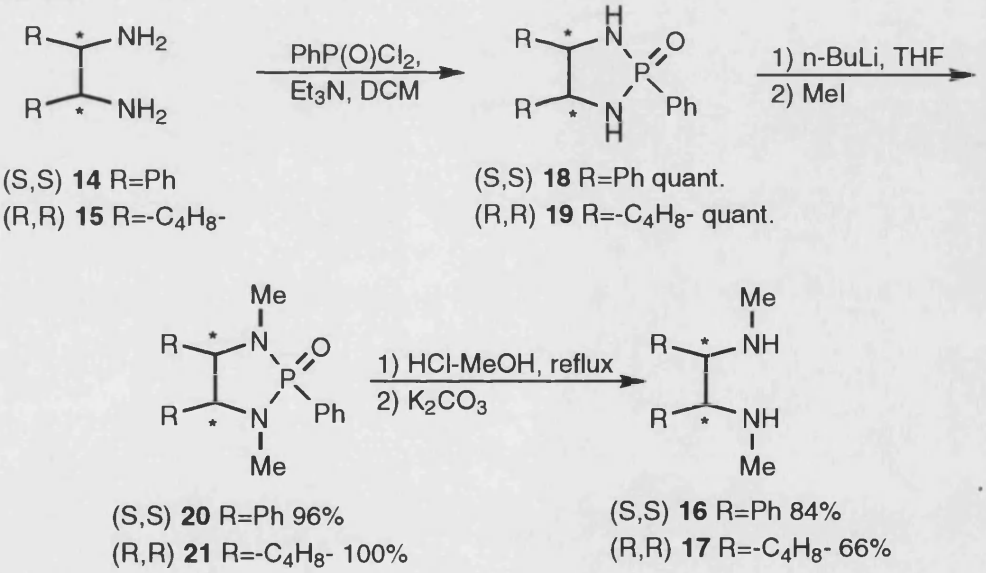
(S,S)-**16** R=Ph
(R,R)-**17** R=-C_4H_8

In order to synthesise the diazaphospholidine oxides a route to the appropriate N,N'-disubstituted C_2-symmetric diamines was required. Methylation of (S,S)-*trans*-1,2-diphenyl ethylene diamine (**14**) and (R,R)-*trans*-1,2-diamino cyclohexane (**15**) using the route described by Alexakis, involving the formation of a bis carbamate followed by LAH reduction (see scheme 1.28) failed to give reasonable quantities of diamines (**16**) and (**17**)

respectively.[1] Consistent problems of incomplete reduction leading to a highly insoluble, cyclic urea prompted a search for another more reliable route to these compounds.

Work by other members of the Wills group at Bath highlighted the possibility of methylating a phenyl diazaphospholidine intermediate and then hydrolysing this to give the desired N,N'-dimethylated diamine.[73] Reaction of diamines (**14**) and (**15**) with phenyl phosphonic dichloride in DCM in the presence of excess triethylamine resulted in the formation of phenyl diazaphospholidine oxides (**18**) and (**19**) in quantitative yield for both cases. Bis-methylation of (**18**) and(**19**) was achieved using n-BuLi in THF at 0°C, to generate the bis anion, and quenching with methyl iodide at 0-20°C gave (**20**) and (**21**) in 96 and 100% yield respectively. The methylated phenyl diazaphospholidine oxides (**20**) and (**21**) could then be hydrolysed in refluxing HCl-methanol to give the corresponding, highly crystalline, diamine hydrochloride salts which were recrystallised from isopropyl alcohol to remove the phosphate ester side product. The pure hydrochloride salts were then converted, by washing with saturated potassium carbonate solution, to the free diamines (**16**) and (**17**) in 84 and 66% yields respectively (see scheme 1.29).

Scheme 1.29:



(S,S) **14** R=Ph
(R,R) **15** R=-C_4H_8-

(S,S) **18** R=Ph quant.
(R,R) **19** R=-C_4H_8- quant.

(S,S) **20** R=Ph 96%
(R,R) **21** R=-C_4H_8- 100%

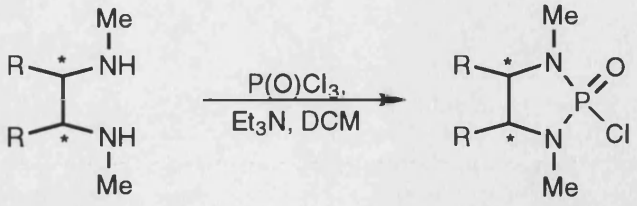
(S,S) **16** R=Ph 84%
(R,R) **17** R=-C_4H_8- 66%

With the desired methylated diamines (**16**) and (**17**) in hand the chloro diazaphospholidine oxide electrophiles (**22**) and (**23**) could be synthesised.[1] Treatment of methylated diamines (**16**) and (**17**) with phosphorus oxychloride in a DCM solution, containing excess triethylamine as an HCl scavenger, gave the chloro diazaphospholidine oxides (**22**) and (**23**), as waxy solids, in 87 and 95% yields respectively (see scheme 1.30).

Synthesis of diazaphospholidine oxide derivatised cleft receptors (**24**) and (**25**) was achieved by the lithiation of urethane (**7c**), using 3 equivalents of s-BuLi-TMEDA in ether at

room temperature for 3 hours, as described previously, and quenching with the chloro diazaphospholidine oxide electrophiles (**22**) and (**23**).

Scheme 1.30:

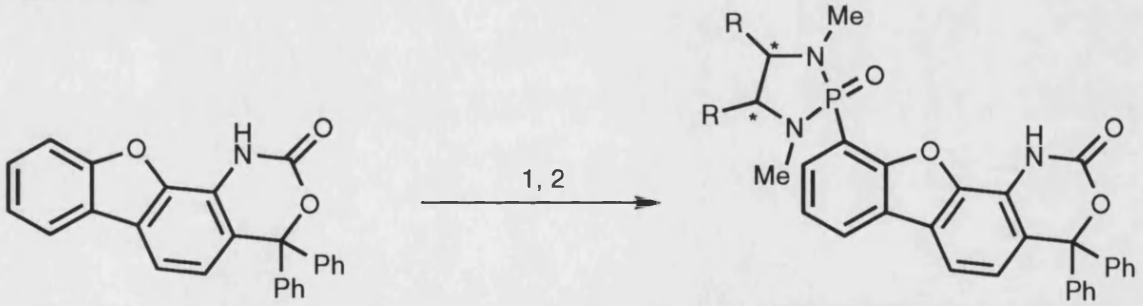


(S,S) **16** R=Ph
(R,R) **17** R=-C_4H_8-

(S,S) **22** R=Ph 87%
(R,R) **23** R=-C_4H_8-95%

Only the dibenzofuran derived urethane (**7c**) was derivatised in this manner because, in general, reactions of the dibenzofuran derived compound were more reproducible than those for the dibenzothiophene analogues and gave more soluble and easier to purify products. Careful purification, by rapid suction flash chromatography, of electrophiles (**22**) and (**23**) was required to ensure that no phosphinic acids were present, as any trace of these appeared to interfere in the derivatisation and dramatically lower the yield. When very pure materials were used the cleft receptors (**24**) and (**25**) were formed in 33 and 63% yield respectively (see scheme 1.31). Again the mass balance for these reactions was accounted for by recovery of the urethane (**7c**).

Scheme 1.31:



7c

(S,S) **24** R=Ph 33%
(R,R) **25** R=-C_4H_8- 63%

1) 3eq 1:1 s-BuLi-TMEDA, ether, -78-20°C, 3hrs; 2) **22** or **23**, THF, -78-20°C, 16hrs.

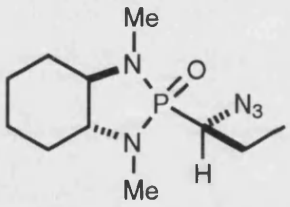
Single crystal X-ray analysis of cleft receptor (**25**) (see fig. 1.19 and Appendix Chapter 3) not only served to confirm the structure of the receptor but also highlighted some interesting properties of the molecule.

Firstly the molecule crystallised as a dimer bridged by two water molecules in a hydrogen bonded array (see fig. 1.20). This unusual feature clearly demonstrated the ability of the P=O and carbamate NH to participate in hydrogen bonding interactions as expected.

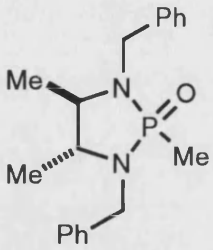
Also evident from the structure was the pseudo-tetrahedral nature of the diazaphospholidine nitrogen atoms, the geometry of which was controlled by the stereochemistry of the bridgehead ring junction. This type of nitrogen geometry and stereochemical information transfer has been well documented for similar diazaphospholidine oxide compounds.

Hanessian and Spilling have noted the ring nitrogen geometry for diazaphospholidine oxides (**26**) and (**27**) (see fig. 1.16).[74, 75] In the case of bicyclic (**26**) the sum of the nitrogen bond angles ΣN was found to be 344° compared to a ΣN of 360° for planar and a ΣN of 328.5° for tetrahedral, thus the geometry was midway between planar and tetrahedral. This distortion from planarity amounted to a displacement of 0.35Å from the plane formed by the neighbouring atoms, (for comparison the P-N bond length was measured as 1.64Å). Interestingly in the case of monocyclic (**27**) the ΣN was found to be 359°, clearly planar. In the case of receptor (**25**) the ΣN value was calculated to be 352°, still appreciably distorted from planarity.

Fig. 1.16:



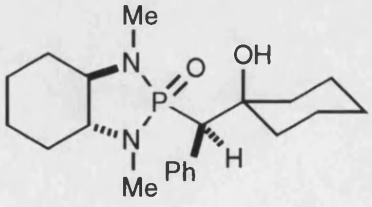
(**26**)



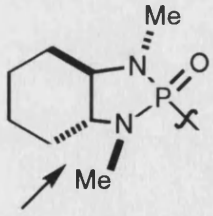
(**27**)

The X-ray structures of (**26**) and a closely related diazaphospholidine oxide (**28**) clearly show that the exocyclic nitrogen substituents are oriented in an opposing manner to the cyclohexyl ring CH_2 groups so as to minimise steric interactions (see fig. 1.17).[76] A similar orientation of the N-methyl substituents is observed in the structure of receptor (**25**).

Fig. 1.17:



(**28**)



N-Me Opposes Ring CH_2 to Minimise Steric Interactions

The final important aspect of the crystal structure is that the diazaphospholidine oxide unit was observed to be significantly twisted away from the plane of the aromatic backbone. Such a phenomenon was also predicted by the molecular modelling studies on simpler amides, as discussed in the introduction. Disappointingly no control over the direction of the

twist, into or out of the plane, was observed in the crystal structure (see fig. 1.20). It had been hoped that the N-methyl group which points down towards the aromatic system might have controlled the direction of the twist, to some extent, by virtue of a steric interaction with the aromatic ring hydrogen (see fig. 1.18). However is was considered possible that crystal packing effects might have overcome any slight steric bias present in the system and that this might still play a role in controlling the solution phase conformation of the molecule. .

Fig. 1.18:

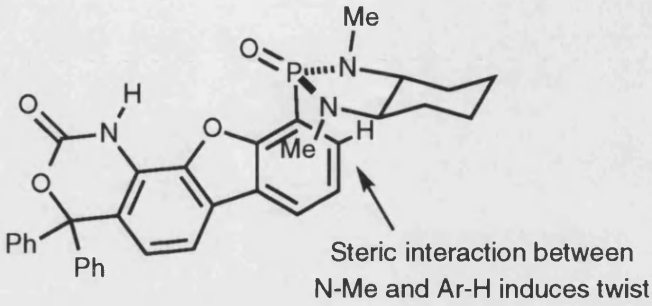


Fig. 1.19:

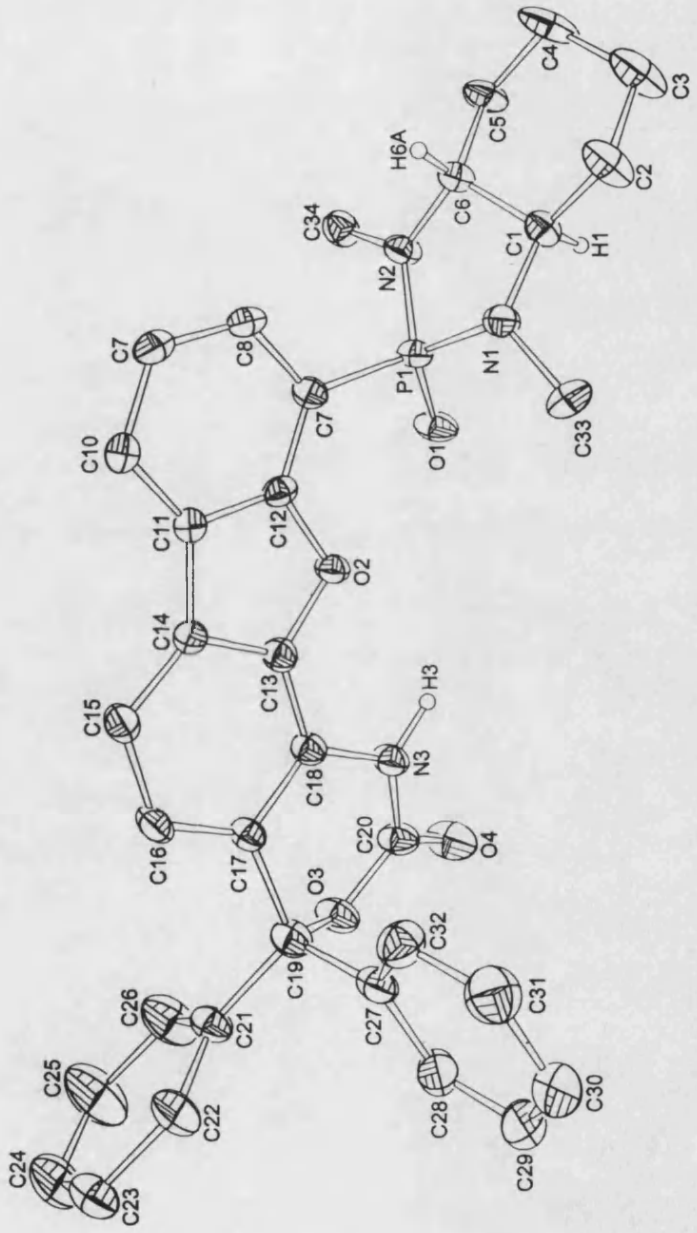
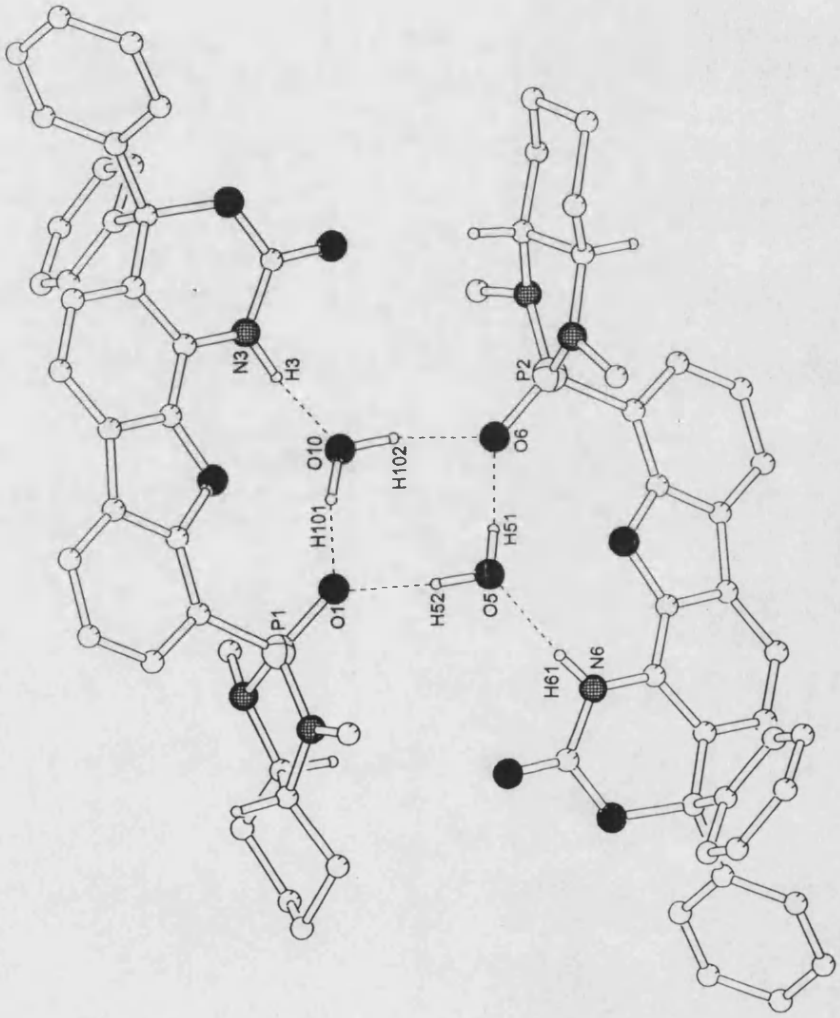

C4
C3
C5
H6A
C2
C6
C34
C1
H1
N2
C7
C8
P1
N1
C7
C33
C10
O1
C11
C12
O2
C14
C13
H3
C15
C18
N3
C16
C17
C20
O4
O3
C32
C19
C31
C26
C21
C27
C25
C22
C28
C30
C24
C23
C29

Fig. 1.20:

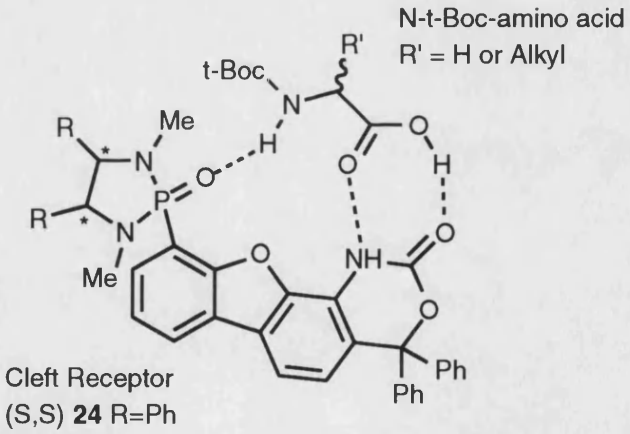


Assessment of Cleft Receptors as Amino Acid Binders

Since the binding interactions between receptor and amino acid were expected to be hydrogen bonding in nature NMR analysis was considered to be a good means of assessing the strength of the interactions. The stronger the hydrogen bond the more deshielded the proton and hence the greater the down field shift of the signal, (see Section 1 Chapter 1 for a discussion on this). In the case of the diazaphospholidine receptors it was envisaged that both ^{1}H and ^{31}P NMR could be employed, since hydrogen bonding interactions involving both the carbamate N-H and the P=O unit were expected to occur. ^{31}P NMR was particularly favoured due to the presence of only one signal in the spectrum, hence avoiding any problems of signal overlap.

Attempts to assess the binding properties of the dibenzothiophene amide receptors (**8b**) and (**8c**) failed due to the very poor solubility of these compounds in $CDCl_3$, (use of $CDCl_3$ was essential due to its low hydrogen bonding capacity compared to solvents such as d6-DMSO or d4-Methanol), thus binding studies concentrated on the diazaphospholidine clefts (**24**) and (**25**) (see fig. 1.21). Here too problems were encountered due to the high affinity of these clefts for water (as seen in the X-ray structure). If any water was present in the NMR sample this bound very strongly to the cleft and precluded any amino acid binding. This problem was circumvented by meticulous drying of the cleft receptor, amino acid, $CDCl_3$ and NMR tubes before making the samples up under an atmosphere of dry nitrogen.

Fig. 1.21:

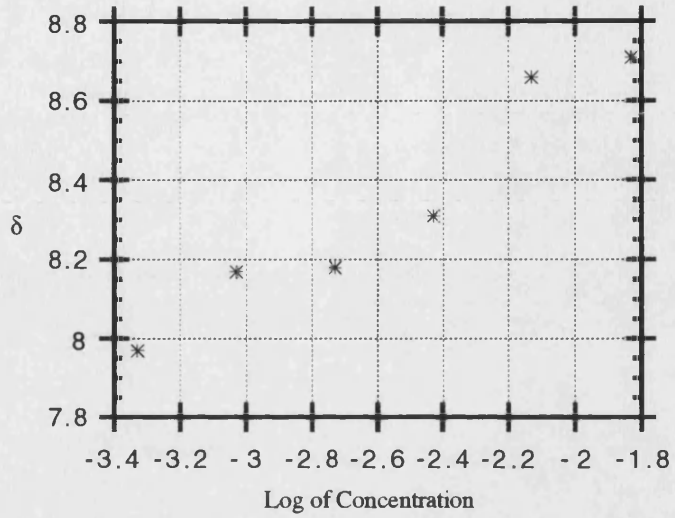


Cleft Receptor
(S,S) **24** R=Ph
(R,R) **25** R=-C_4H_8-

The first task was to determine a value of the Critical Association Constant (CAC) for the diazaphospholidine clefts so that binding studies could be carried out at a concentration where no appreciable self complexation of the clefts was occurring. A ^{1}H NMR dilution study of cleft (**24**) was carried out in $CDCl_3$ and the CAC determined to be at 1.85×10^{-3}M from the point of inflexion on the graph (see graph 1.1).

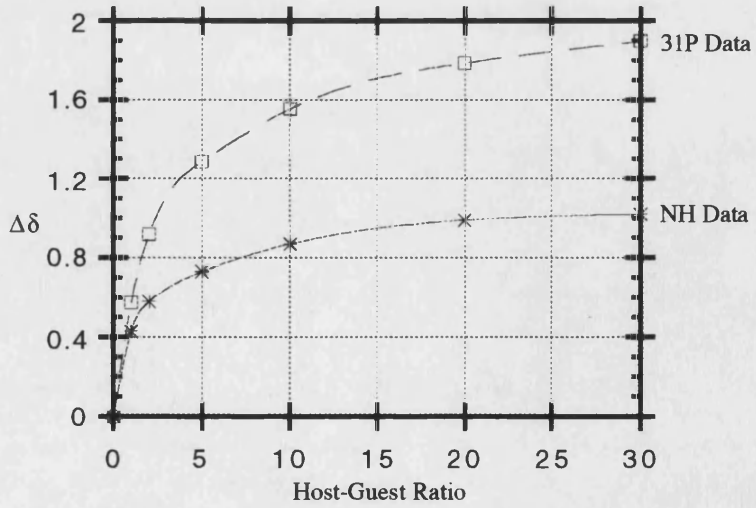
Graph 1.1:

Determination of the CAC value for (**24**) in $CDCl_3$ solution. Inflexion at -2.73 gives a CAC of $1.85x10^{-3}M$.



Graph 1.2:

NMR titration study of (**24**) with N-Boc-glycine in $CDCl_3$ (working at a concentration of $1.48x10^{-3}M$). For the NH data half complexation was found to be at 1.5 equivalents of guest, giving $K = 676M^{-1}$. For the ^{31}P data half complexation was found at 2.0 equivalents of guest, giving $K = 450M^{-1}$. Thus an average value of $K_{av} = 560M^{-1}$ was determined in this case.



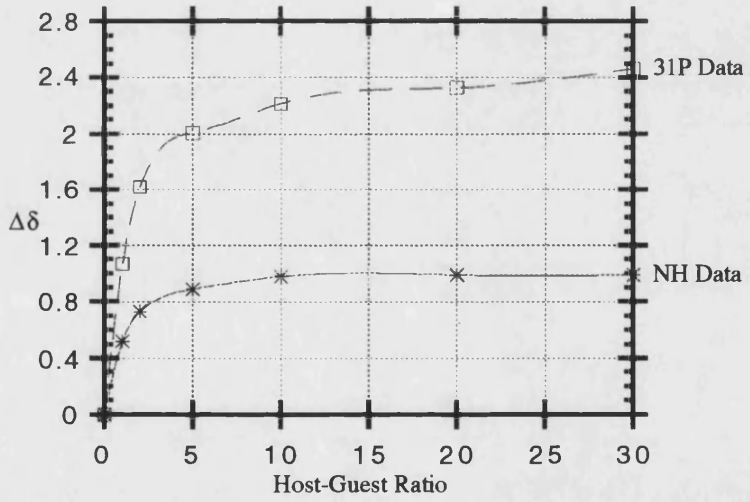
Binding of cleft (**24**) to N-t-Boc-glycine was then investigated at a concentration ($1.48x10^{-3}M$) below that of the CAC. On addition of increasing amounts of amino acid an appreciable down field shift in both the urethane N-H and P=O signals was observed. From the data

obtained in the ^{1}H and ^{31}P NMR experiments an average value for the association constant K_{av} was calculated as $560M^{-1}$ (see graph 1.2).

For a comparison of the binding abilities of clefts (**24**) and (**25**), the binding of cleft (**25**) to N-t-Boc-glycine was also assessed by ^{1}H and ^{31}P NMR. A value of $K_{av} = 930M^{-1}$ was determined in this case (see graph 1.3). The higher the value of K the more the binding equilibrium is shifted over towards complexation, indicating a stronger binding interaction. Clearly cleft (**25**) was the stronger binder and thus further studies on binding of this cleft to chiral amino acid derivatives were then undertaken.

Graph 1.3:

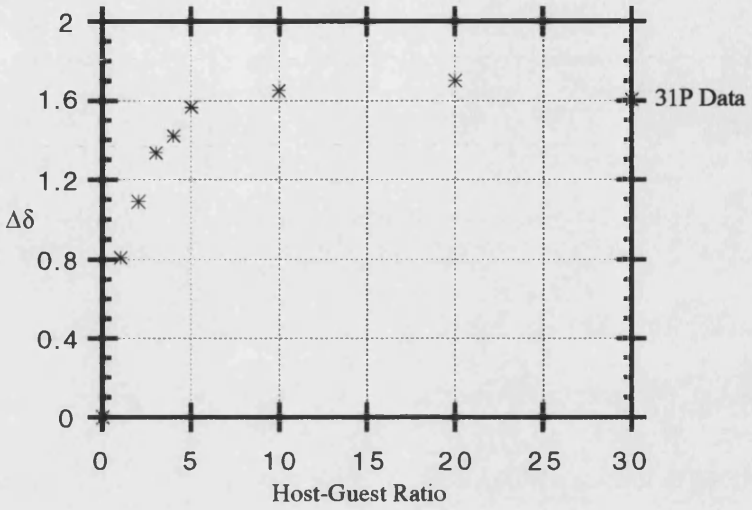
NMR titration study of (**25**) with N-Boc-glycine in $CDCl_3$ (working at a concentration of $1.74x10^{-3}M$). For the NH data half complexation was found to be at 1.06 equivalents of guest, giving $K = 1030M^{-1}$. For the ^{31}P data half complexation was found at 1.2 equivalents of guest, giving $K = 820M^{-1}$. Thus an average value of $K_{av} = 930M^{-1}$ was determined in this case.



Using ^{31}P NMR analysis the binding of cleft (**25**) to N-t-Boc-D and L-alanine was investigated. In the case of N-t-Boc-D-alanine a value of $K = 1030M^{-1}$ was determined (see graph 1.4). Binding to N-t-Boc-L-alanine was weaker giving a value of $K = 440M^{-1}$ under identical conditions (see graph 1.5). This difference in binding constants amounted to an enantiomeric excess of binding in the region of 40% in favour of N-t-Boc-D-alanine.

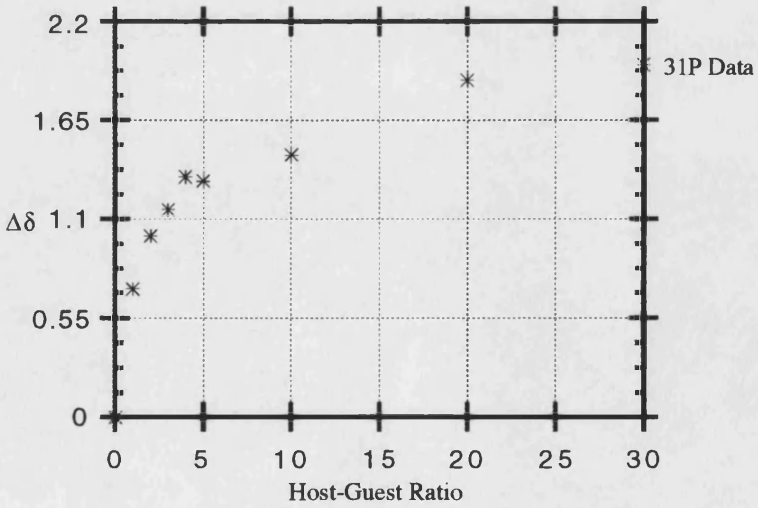
Graph 1.4:

NMR titration study of (**25**) with N-Boc-D-Alanine in $CDCl_3$ (working at a concentration of $1.74x10^{-3}M$). For the ^{31}P data half complexation was found at 1.06 equivalents of guest, giving $K = 1030M^{-1}$.



Graph 1.5:

NMR titration study of (**25**) with N-Boc-L-Alanine in $CDCl_3$ (working at a concentration of $1.74x10^{-3}M$). For the ^{31}P data half complexation was found at 1.8 equivalents of guest, giving $K = 440M^{-1}$.



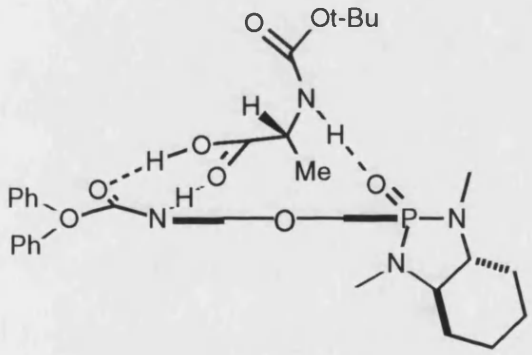
This result, in favour of binding to the D-alanine derivative, can be rationalised by considering a model for the binding interaction based on; the results from the X-ray structure

of cleft (**25**); and the possible steric factors affecting solution phase conformations of N-t-Boc protected amino acids discussed in Section 1 Chapter 1.

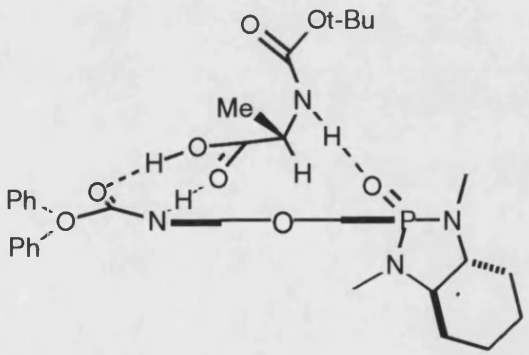
The X-ray of (**25**) showed clearly a twisted conformation where the diazaphospholidine oxide unit had rotated away from the plane of the aromatic system. As discussed earlier it is possible that the direction of the twisting could be controlled, in the solution phase, by the orientation of the N-Me groups on the diazaphospholidine oxide. If this is considered to be the case then upon binding of receptor (**25**) to N-t-Boc-D or L-Alanine diastereomeric complexes would form as a result of the axial chirality of the receptor. It would be expected that the two diastereomeric complexes would differ in stability and hence one should form preferentially, this would be reflected by a difference in binding constants which is indeed the case. The fact that N-t-Boc-D-Alanine forms the most stable complex in this case can be rationalised by the model shown in fig. 1.22, which is based on preferred solution phase conformations of N-t-Boc protected amino acids as discussed in Section 1 Chapter 1.

Fig. 1.22:

Viewing the Receptor-Amino Acid Complex From Above.



D-Alanine Me is Pseudo Equatorial
Favoured



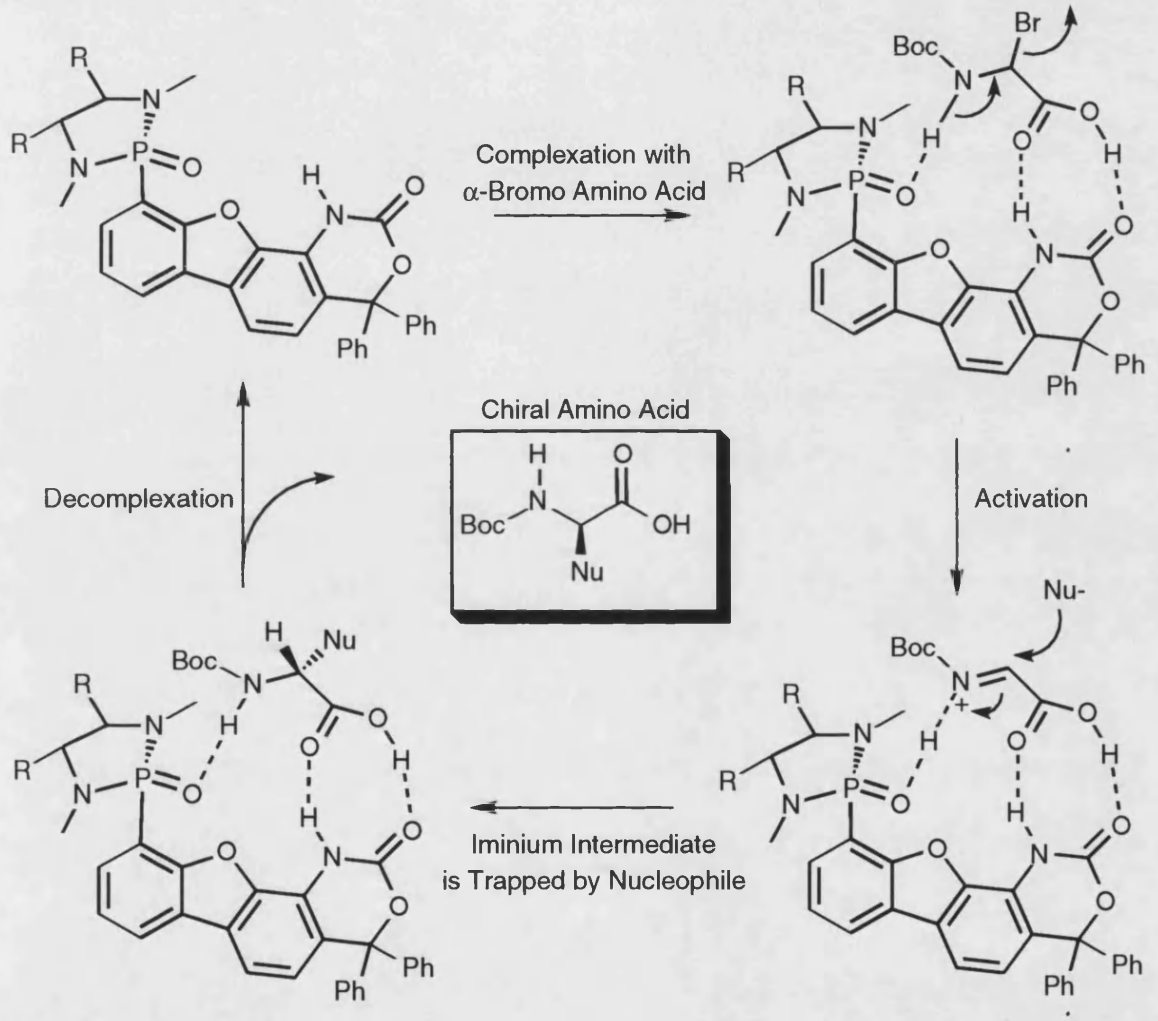
L-Alanine Me is Pseudo Axial
Disfavoured

The possibility that larger substituents, on the nitrogen atoms of the diazaphospholidine oxide unit, could enhance the enantioselectivity of binding was briefly investigated. Synthesis of (R,R)-N,N'-diisopropyl-1,2-diamino cyclohexane was achieved by hydrogenation of the diamine (**15**) in the presence of acetone.[1] The N,N'-dibenzylated equivalent was synthesised via a reductive amination in the presence of benzaldehyde.[77] Both of these diamines could be converted to the corresponding chloro diazaphospholidine oxides in good yield, however they proved totally unreactive as electrophiles in the lithiation of (**7e**) probably due to increased steric hindrance.

Application of Cleft Receptor (**25**) in Asymmetric Synthesis

Having established that the cleft receptor (**25**) was not only capable of binding to amino acid derivatives, but also of some degree of enantioselection during binding, it was hoped that the receptor could be employed as a catalyst for the asymmetric synthesis of amino acids, as outlined in Section 1 Chapter 3 (see scheme 1.32).

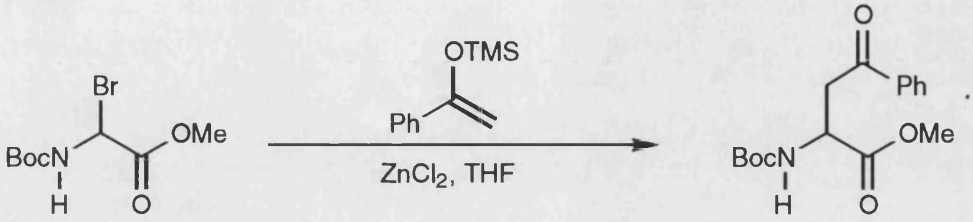
Scheme 1.32:



The test case chosen for this study was the reaction of N-t-Boc-(α)-bromo-glycine methyl ester (**29**) with the TMS-enol ether of acetophenone to form amino acid (**30**) (see scheme 1.33). The glycine methyl ester (**29**), (prepared by a photolytic bromination of N-t-Boc-glycine methyl ester), was chosen as substrate because the corresponding acid could not be synthesised. Numerous attempts to synthesise both the α-bromo and α-acyl derivative of the free acid failed to yield any products. (**29**) was never the less considered to be capable of binding to the cleft receptor (**25**) *via* two hydrogen bonding interactions, between the P=O of the diazaphospholidine and N-H of (**29**) as well as between the N-H of the urethane and the C=O of the methyl ester.

Williams and co-workers reported a Lewis acid catalysed procedure for the synthesis of (**30**) using zinc chloride to activate the bromide.[57] Use of this procedure to synthesise (**30**) worked well giving a colourless oil in 84% yield, which was determined, by a variety of analytical techniques, to be the desired product. This sample provided a useful means of comparison, by t.l.c. and NMR, for the products of the diazaphospholidine oxide catalysed reactions.

Scheme 1.33:

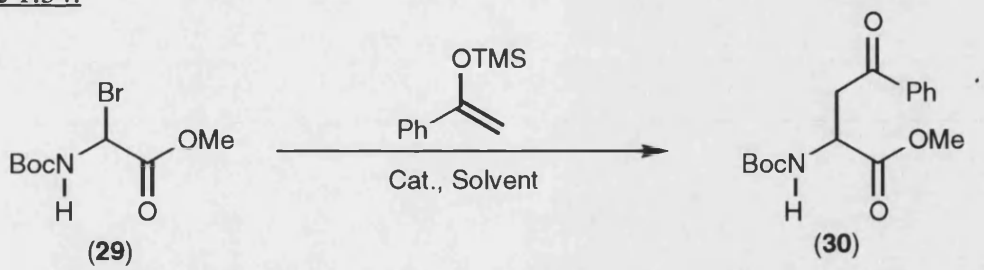


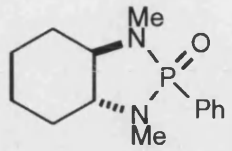
(**29**) (**30**)

The key to the catalytic activity of the diazaphospholidine oxide receptor was considered to be the ability of the P=O group to hydrogen bond to the amino acid N-H and activate the bound bromo-amino acid towards formation of an intermediate iminium species (see scheme 1.32). Hence catalytic activity should relate directly to the basicity of the P=O unit. For this reason the structurally related molecules HMPA, known to be a good Lewis base[7], and phenyl diazaphospholidine oxide (21) were also investigated as potential catalysts (see scheme 1.34 and table 1.4).

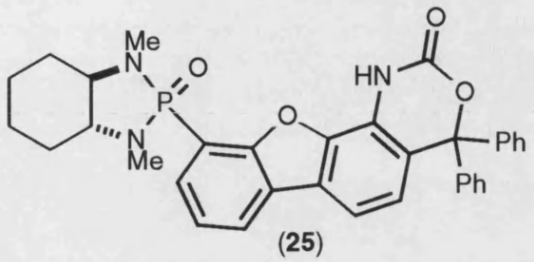
When 1 mole equivalent of HMPA in DCM solution was employed as catalyst the amino acid (**30**) was formed in 25% yield after 16hrs at room temperature. Encouraged by this result 1 mole equivalent of diazaphospholidine oxide (**21**) was then used as catalyst in the reaction to give 39% yield of (**30**). This was a little surprising since HMPA was known to be more basic and thus expected to interact more strongly with the N-H of (**29**). More surprising still was the result obtained when 0.1 mole equivalents of (**21**) were used under identical conditions to give 66% yield of (**30**). Also worth noting is the fact that the products formed in the latter two cases, where the chiral diazaphospholidine oxide (**21**) was employed, did not exhibit any optical activity.

Scheme 1.34:





(21)



(25)

Table 1.4:

Catalyst	Mol. Equivs.	Solvent	Time (hrs)	Yield of **30** (%)
$ZnCl_2$	1.2	THF	3	84
HMPA	1.0	DCM	16	25
21	1.0	DCM	16	39
21	0.1	DCM	16	66
None	-	DCM	16	85
25	0.1	DCM	48	24

At this stage it was considered possible that HMPA and (**21**) were acting as inhibitors of the desired reaction rather than as catalysts. This indeed proved to be the case because, when the uncatalysed reaction was attempted a yield of 85% of (**30**) was achieved after 16hrs at room temperature. No clear explanation for this inhibitory behaviour could be found, however one possibility is that the P=O groups of HMPA and (**21**) were interacting competitively with the TMS-enol ether and thus the pathway for activation of the bromo-amino acid was blocked. An example of the interaction of HMPA and related phosphoramides with the silicon atom of allyl trichlorosilane has recently been reported by Denmark.[7] Cleft receptor (**25**) proved to be by far the most effective inhibitor of the reaction, when 0.1 mole equivalents was used only 24% yield of (**30**) was achieved after 48hrs at room temperature!

With such disappointing initial results it was decided that efforts should be concentrated on the application of structurally related P-(III) diazaphospolidines as chiral ligands for palladium and their use in palladium catalysed allylic substitution reactions. This is the subject of Section 2 of the Thesis.

Section 2

SECTION 2:

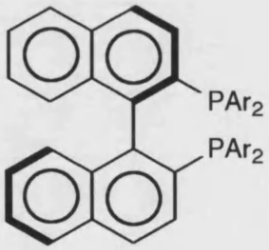
CHAPTER 1: APPLICATION OF PHOSPHINE CONTAINING LIGANDS IN ASYMMETRIC SYNTHESIS

Phosphine containing ligands have been applied extensively to a variety of metal catalysed asymmetric transformations in recent years .[78, 79] This section of the Thesis will concentrate on the use of chiral phosphine containing ligands in palladium catalysed allylic substitution reactions, but before discussing this in more detail some of the other reaction types for which phosphine ligands have been employed will be briefly overviewed.

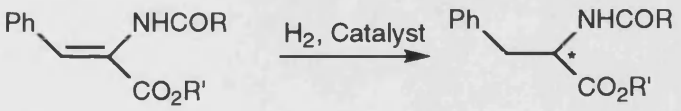
Asymmetric Hydrogenation

Diphosphine ligands for ruthenium and rhodium have been used to great effect in the asymmetric hydrogenation of prochiral double bonds.[79] Perhaps one of the most famous and widely used ligands of this type is Noyori's BINAP ligand.[80] A ruthenium complex of this ligand has been employed in the asymmetric hydrogenation of enamide precursors to amino acids with an impressive degree of enantioselectivity (see scheme 2.1).

Scheme 2.1:



(R)-BINAP

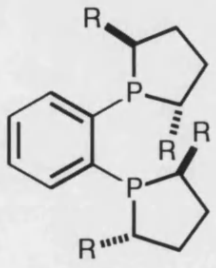


Catalyst = (R)-BINAP-Ru-$(OCOMe)_2$

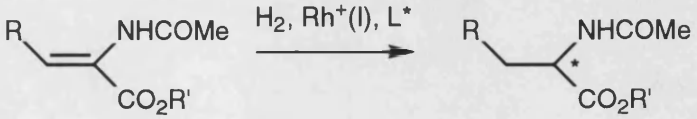
Yield = 100% e.e = 80-100%

More recently Burk and co-workers have reported the use of novel bisphospholane ligands for rhodium in the asymmetric hydrogenation of acetamidoacrylates to give amino acids also with a high degree of enantioselectivity (see scheme 2.2).[81]

Scheme 2.2:



R = Me, Et, iPr

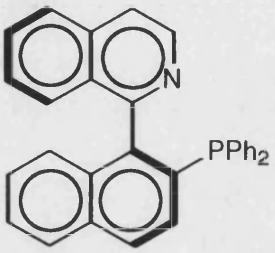


Yield = 100% e.e up to 99%

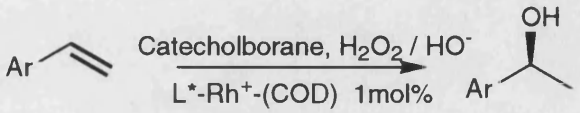
Hydroboration

Brown and co-workers have reported the use of a bidentate phosphine/nitrogen ligand, QUINAP, for the asymmetric hydroboration of styrene analogues in the presence of rhodium.[82] The product benzylic alcohols were obtained in average to good enantioselectivities (see scheme 2.3).

Scheme 2.3:



(S)-QUINAP

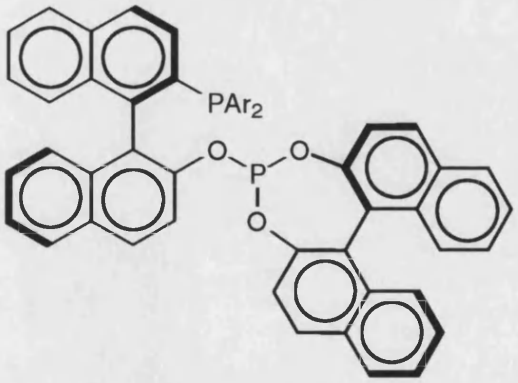


Yield = 56-69% e.e. = 78-94%

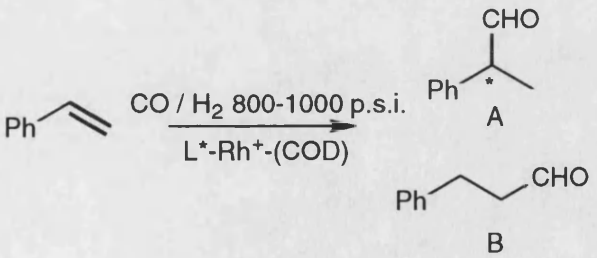
Hydroformylation

Takaya and co-workers have developed the use of a BINAP derived ligand, BINAPHOS, for the asymmetric hydroformylation reaction in the presence of catalytic amounts of rhodium.[83] Hydroformylation of styrene derivatives was shown to proceed with a good degree of regioselectivity and moderate enantioselectivity (see scheme 2.4).

Scheme 2.4:



(R,S)-BINAPHOS



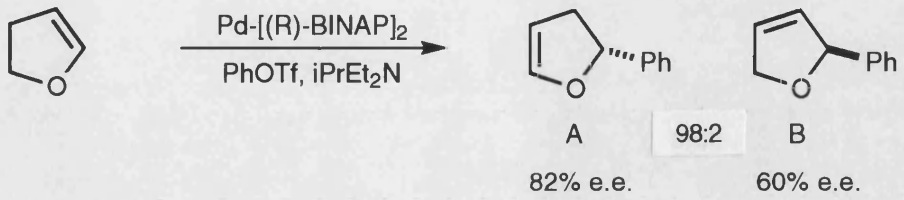
Yield = 94% 90:10 ratio of A to B
80-90% e.e.

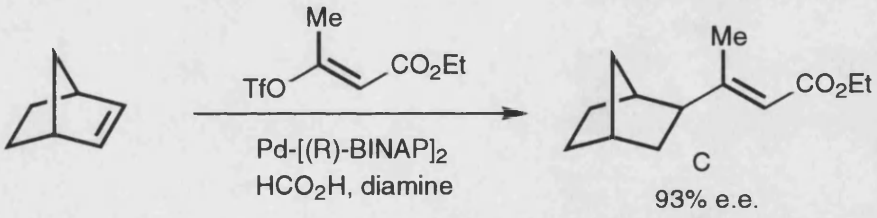
Asymmetric Heck Reactions

Aryl and vinyl triflates have been coupled with alkenes to give enantiomerically enriched products using a BINAP-palladium complex. The reaction of dihydrofuran with phenyl

triflate gave the regioisomeric products A and B in a ratio of 98:2 and in 82 and 60% e.e. respectively (see scheme 2.5).[84]

Scheme 2.5:





Norbornene was shown to react with a vinyl triflate in the presence of the same BINAP-palladium complex to give C in an impressive 93% e.e. (see scheme 2.5).[85]

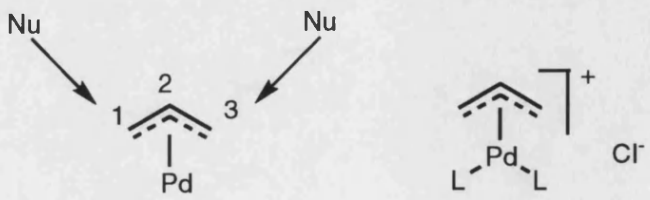
Palladium Catalysed Allylic Substitution

As part of an ongoing project within the Wills group it was decided that initial studies using the proposed diazaphospholidine ligands (as discussed in the General Introduction) should focus on the palladium catalysed allylic substitution reaction.[86] Before discussing the diazaphospholidine ligands in more detail some aspects of the palladium catalysed allylic substitution reaction will be addressed.

Mechanism of Allylic Substitution

In general the palladium catalysed allylic substitution reaction involves the attack of a nucleophile at either terminus of the palladium-allyl complex (see fig. 2.1).

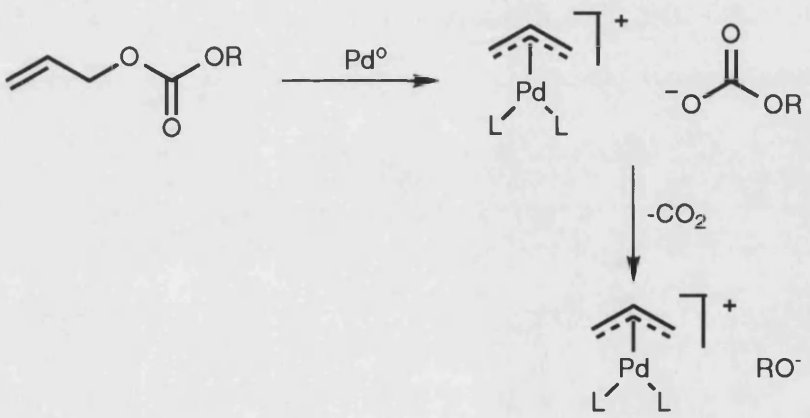
Fig. 2.1:



Early studies of this type of substitution reaction highlighted some important features which have enabled the development of catalytic and asymmetric versions of the reaction.[87] Firstly π-allyl-palladium complexes are relatively unreactive to nucleophiles when present as their chloride dimers but addition of phosphine ligands serves to break up the dimers and increase reactivity. Secondly a ratio of two phosphine ligands per palladium gave optimal performance suggesting that the active species comprises of a cationic complex with chloride as the counterion (see fig. 2.1).

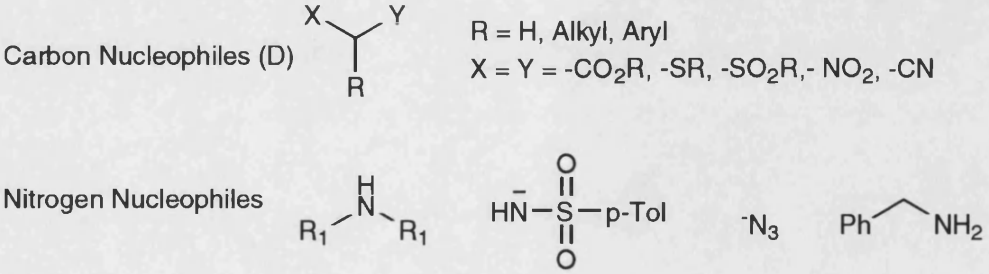
Thirdly it was observed that Pd^0 could be used directly to form the allyl complexes when alkenes possessing a good leaving group (X), at the allylic position, were added to the reaction mixture. Typically X = OAc or OCO_2R have been employed and in these cases the acetate or alkoxy groups generated during the complex formation can act as bases to deprotonate the nucleophile *in situ* (see scheme 2.6).

Scheme 2.6:



The types of nucleophile that are appropriate for use in the allylic substitution reaction are generally soft carbon nucleophiles and amines. The carbon nucleophiles usually possess the general structure D (see fig. 2.2) where R = H, Alkyl or Aryl and X and Y are anion stabilising groups such as: $-CO_2R$, -C(O)R, -SR, -S(O)R, $-SO_2R$, $-NO_2$, -CN.

Fig. 2.2:

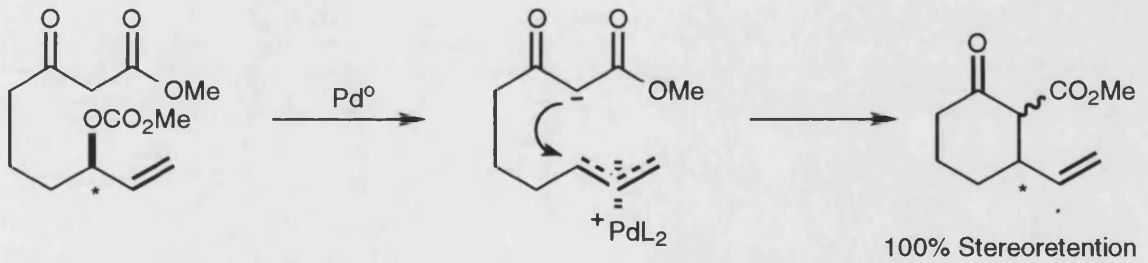


In general amine nucleophiles are restricted to secondary amines, amides, sulfonamides and azides. With the exception of benzylamines the use of primary amines and ammonia as nucleophiles has yielded poor results to date.

Enantioselective Allylic Substitutions

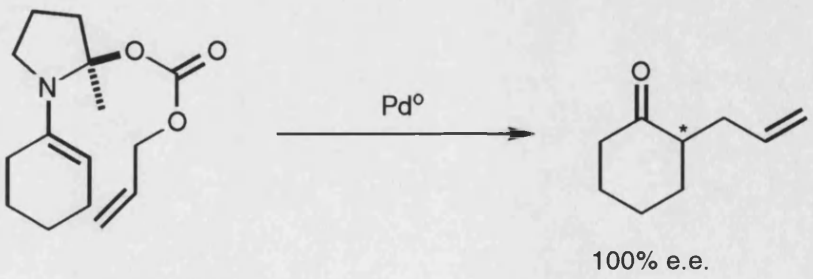
Once the basic features of the allylic substitution reaction had been elucidated attempts at achieving some degree of enantioselectivity in the process could then be undertaken. Three basic approaches to stereoinduction in the allylic substitution reaction have been explored. The first involves the use of a substrate containing a chiral centre at the allylic position. This method relies on stereospecific, oxidative addition of the palladium species followed by stereospecific attack of the nucleophile to give a chiral product with net retention of stereochemistry. Tsuji and co-workers demonstrated this strategy to good effect with the palladium mediated cyclisation of optically pure methyl (R)-3-oxo-7-(methoxycarbonyloxy)-8-nonenoate to an allyl cyclohexanone with complete retention of stereochemistry at the original chiral centre (see scheme 2.7).[88]

Scheme 2.7:



The second approach involves the use of a chiral leaving group in the allylic substrate or a chiral nucleophile to effect stereocontrol in the substitution reaction. Hiroi and co-workers successfully employed a chiral enamine as the nucleophile in an intramolecular allylation reaction giving the product in 100% optical yield (see scheme 2.8), an intermolecular version of this reaction gave products in moderate optical yields of approximately 50%.[89]

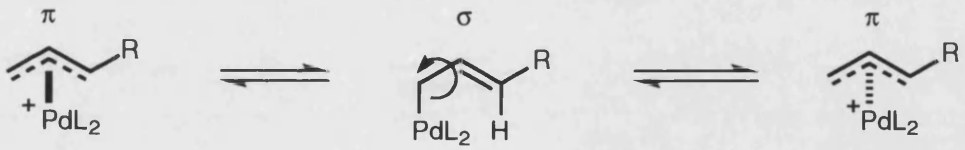
Scheme 2.8:



The third and final approach has perhaps enjoyed the most interest in recent years. This involves the use of a chiral, bidentate ligand for palladium and can achieve enantioselectivity in one of two ways. A prochiral allyl ligand can react with a chiral palladium-ligand complex to form two diastereomeric species which react with the nucleophile at different rates leading to formation of enantiomerically enriched products. Alternatively an achiral, meso, allyl ligand can react with the palladium-ligand complex to form a chiral π-allyl species, in this case the transition states leading to nucleophilic attack at either allylic terminus are diastereomeric and can result in the formation of optically active products.

Where chiral ligands have been used to induce enantioselectivity the *in situ* racemisation of the palladium-allyl intermediate has often resulted in a reduction in the degree of stereoselection achieved. Racemisation can occur in a variety of ways, for example when the allyl ligand possesses a substituent at only one terminus, the palladium complex can be subject to *syn-anti* isomerisation (see fig. 2.3) resulting in the rapid interconversion of the π-facial isomers.

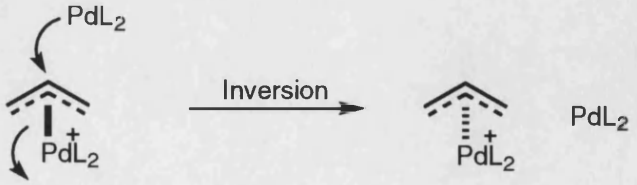
Fig. 2.3:



Rotation is Possible

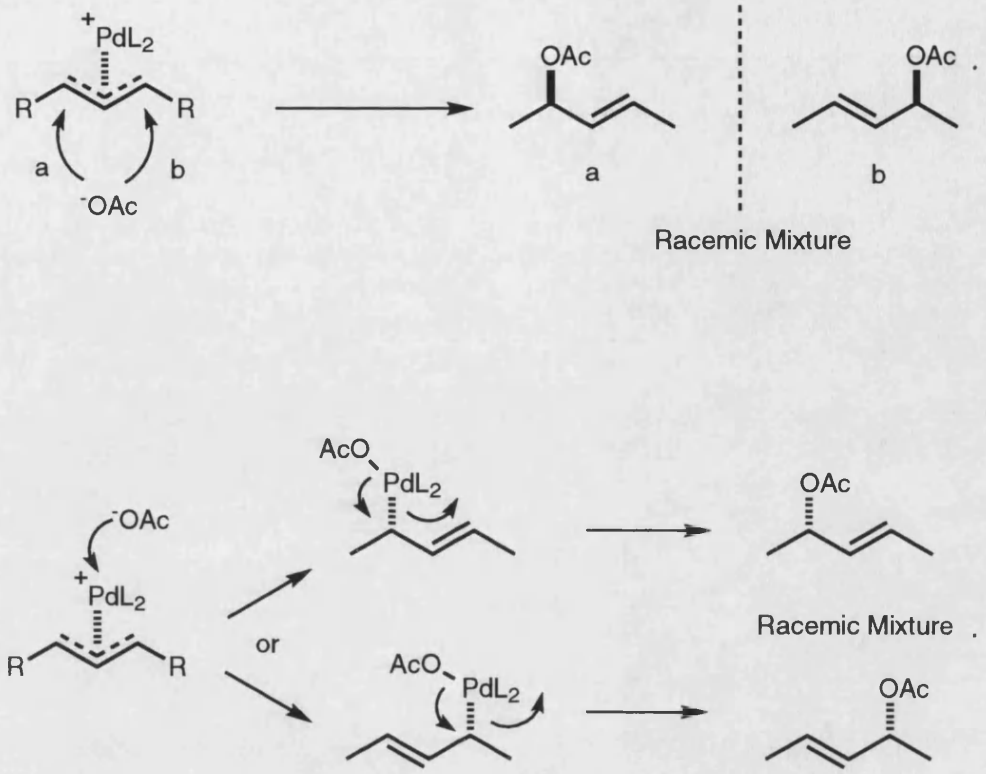
Another process of racemisation involves the attack by a palladium-ligand complex on the allyl moiety of an allyl-palladium species resulting in the formation of an enantiomeric allyl-palladium species (see fig. 2.4) this is particularly a problem when a high concentration of palladium-ligand complex is present in solution.

Fig. 2.4:



Finally racemisation of the allylic precursors to meso, allyl species can be achieved by reaction of the displaced X group with the allyl-palladium species to regenerate the precursor.

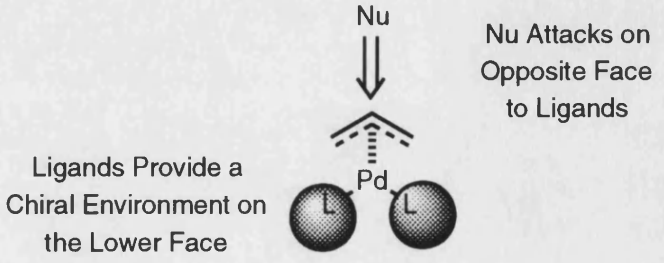
Fig. 2.5:



This can involve attack of X at either terminus of the allyl ligand, on the opposite face to the palladium, or attack of X directly on palladium followed by reductive elimination to reform the precursor with net racemisation occurring (see fig. 2.5). In certain cases this process has been used to advantage to achieve dynamic kinetic resolution of a racemic allylic precursor enabling the substitution reaction to proceed to greater than 50% completion.

One final problem that has to be overcome in order to achieve stereoinduction is that nucleophilic attack on the allyl-palladium-ligand complex usually occurs on the face of the allyl unit opposite to the palladium (*exo*) and hence remote from the chiral environment of the ligand (see fig. 2.6). A variety of approaches have been used to overcome this problem and these will now be discussed in some detail.

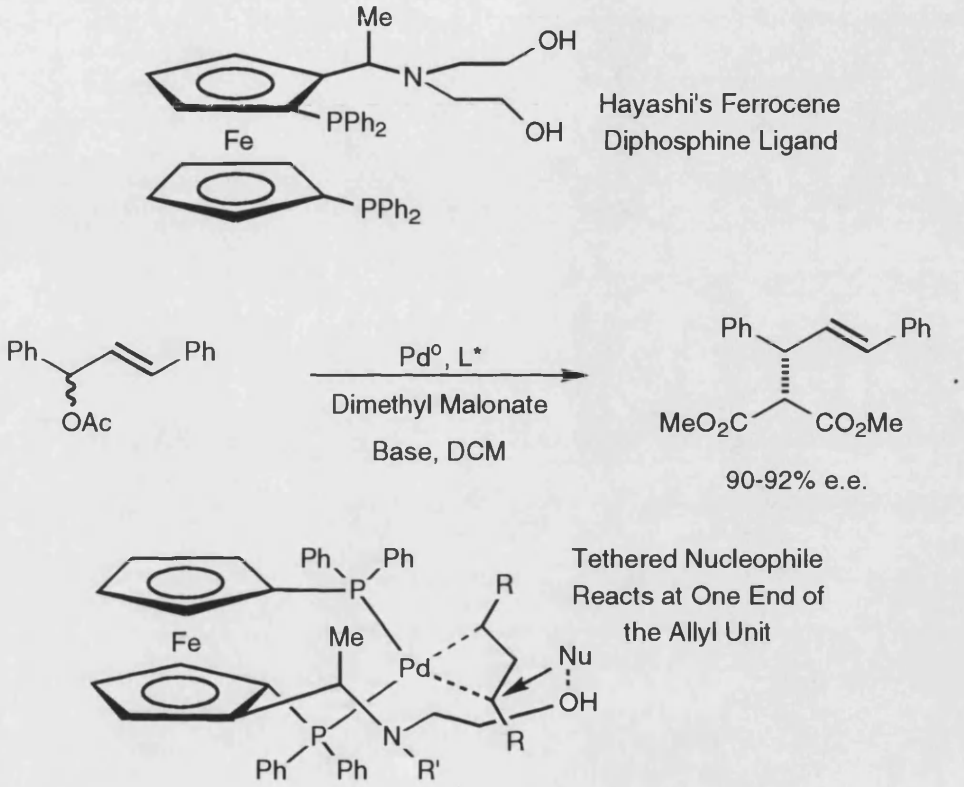
Fig. 2.6:



Chiral Ligands for Asymmetric Allylic Alkylation

Hayashi reported the use of a chiral diphosphine ligand derived from ferrocene for the allylic alkylation of meso, allyl species with high enantioselectivity (>90%) (see scheme 2.9).[90]

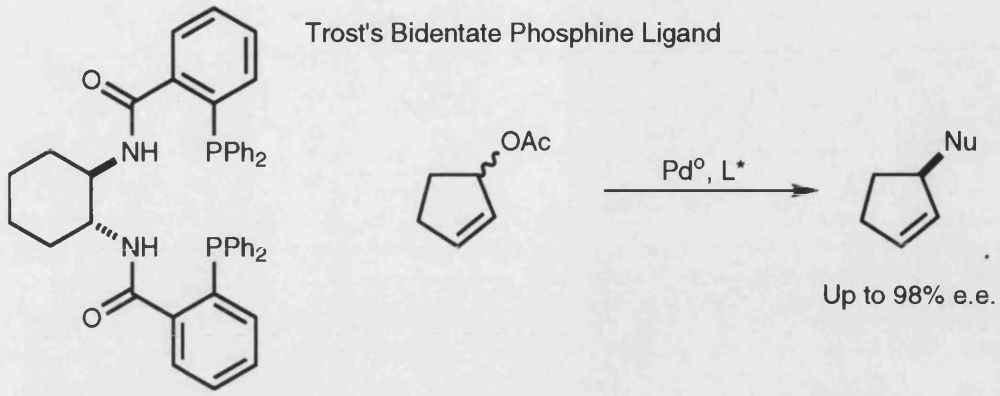
Scheme 2.9:



The ligand possesses an extended tether which is thought to aid in the stereocontrol of the nucleophilic addition by coordinating to the nucleophile and thus extending the influence of the chiral ligand to the *exo* face of the allyl unit (see scheme 2.9).

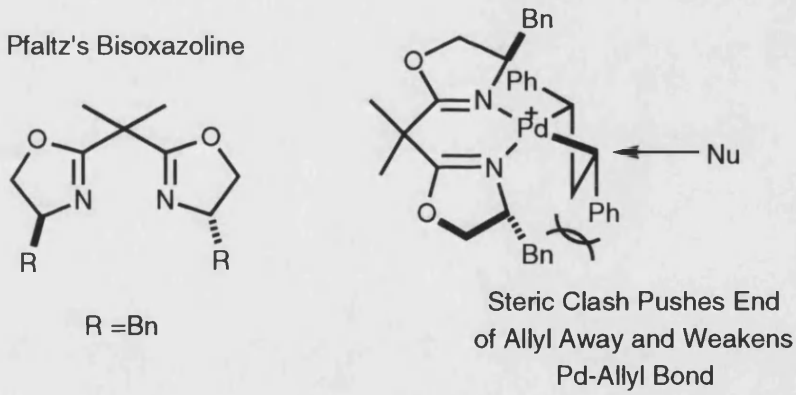
Another successful approach to stereocontrol in the alkylation reaction has been developed by Trost and co-workers using diphosphine ligands with an extended chiral sphere of influence surrounding the centrally coordinated palladium atom (see scheme 2.10).[91] This ligand type has been very successful for the alkylation of cyclic, meso, allyl substrates giving enantioselectivities of up to 98%. It is thought that a propeller arrangement of the phenyl groups on the phosphines serves to create a rigid chiral environment which favours the formation of only one of the two possible palladium-allyl intermediates hence leading to a high degree of stereocontrol.

Scheme 2.10:



Pfaltz has pioneered the use of C_2-symmetric bis-oxazolines for allylic substitution reactions (see fig. 2.7).[92] These ligands have shown great promise for the alkylation of meso, allyl species giving enantioselectivities of greater than 90% in some cases. It is thought that the stereocontrol arises from the slightly distorted coordination of the allyl system to palladium resulting in a lengthening of one of the Pd-allyl bond distances (see fig. 2.7). This longer, weaker bond is thus expected to break preferentially during nucleophilic attack leading to formation of an enantiomerically enriched product.

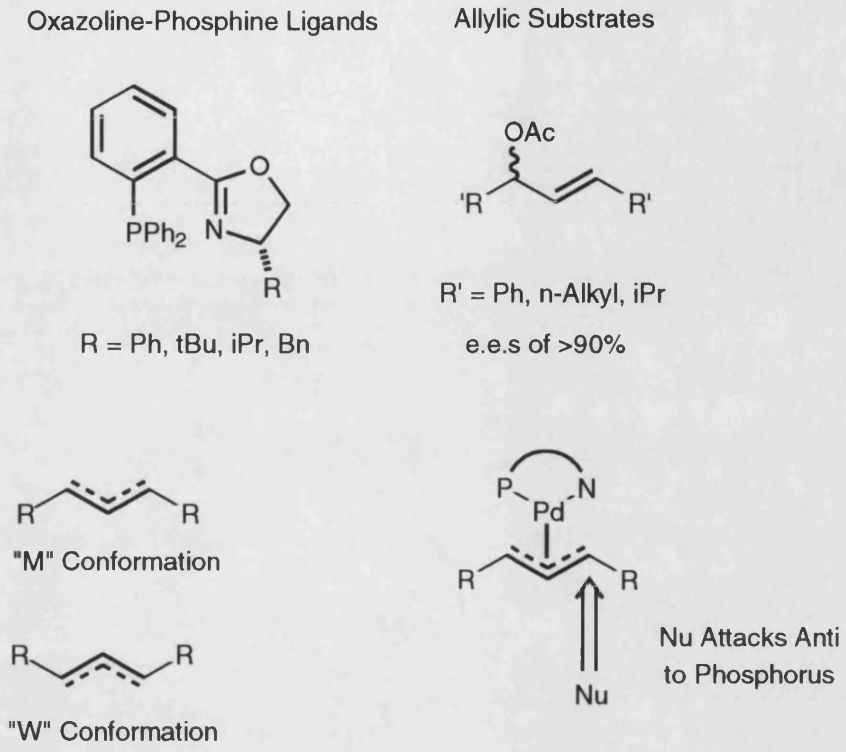
Fig. 2.7:



The final and perhaps most successful approach to the problem of stereocontrolled allylic substitution has been the use of heteronuclear bidentate ligands such as the oxazoline-phosphines developed by Pfaltz, Helmchen and Williams (see fig. 2.8) and the QUINAP ligand developed by Brown (see earlier discussion on hydroborations).[93, 94] These ligands have been used successfully for the allylic alkylation of meso, allyl systems with very high enantioselectivities (>90%) and in good yield. The source of stereoselection in these ligands is more complex resulting from both the control of the preferred conformation of the allyl coordinated to the palladium (either "M" or "W") and the terminus at which nucleophilic attack occurs. The stronger *trans* labilising effect of the phosphorus ligand results in a

weakening of the Pd-allyl bond *anti* to the phosphorus and hence nucleophilic attack at that terminus will be preferred (see fig. 2.8).

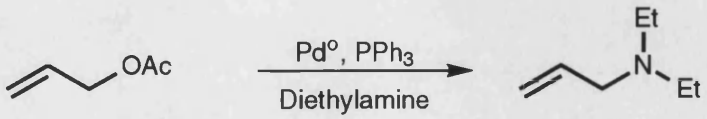
Fig. 2.8:



Enantioselective Allylic Amination Reactions

Palladium catalysed allylic substitutions are not restricted to carbon based nucleophiles, indeed one area which has seen some attention in recent years is the use of nitrogen based nucleophiles. The first example of a reaction of this type was reported by Atkins in 1970 when he used diethylamine as a nucleophile in the allylic substitution of allyl acetate (see scheme 2.11).[95]

Scheme 2.11:



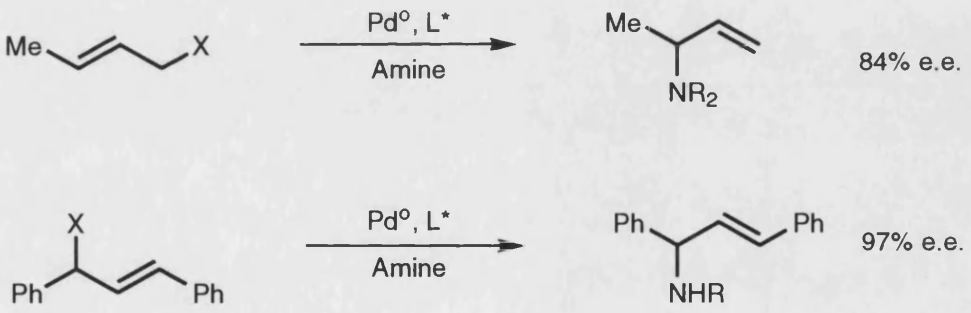
Since that time a large number of nitrogen nucleophiles have been employed in the allylic amination reaction to good effect (see table 2.1).

Table 2.1:

Nitrogen Nucleophile	Researcher	Reference
Benzylamine	Tanigawa	96
Morpholine	Tanigawa	96
Piperidine	Genet, Takahashi	97, 98
Dimethylamine	Genet	97
Pyrrolidine	Tamura, Nwokoga	99, 100
Tosylamide	Backwall	101
$(Boc)_2NH$	Conell	102
Sodium Azide	Murahashi	103

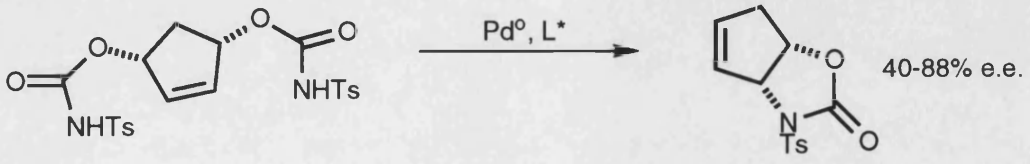
In 1989 Hayashi reported an asymmetric amination reaction using his ferrocene based diphosphine ligand (see earlier) to give aminated products with enantioselectivities of up to 97% (see scheme 2.12). [104]

Scheme 2.12:



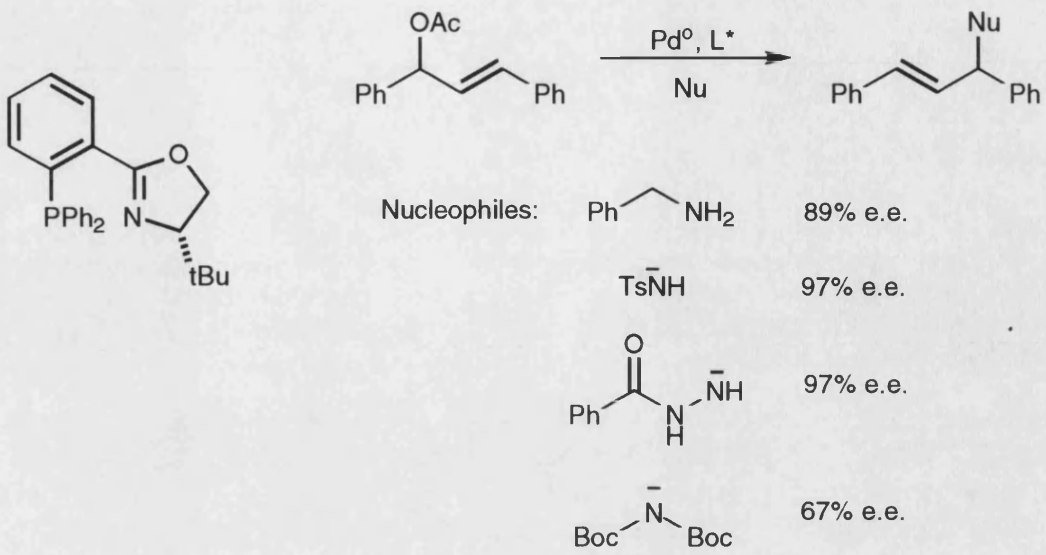
Other examples of asymmetric amination soon followed; Trost reported the intramolecular amination of a cyclic, meso, allyl precursor using his extended diphosphine ligand to give up to 80% enantiomeric excess (see scheme 2.13).[105]

Scheme 2.13:



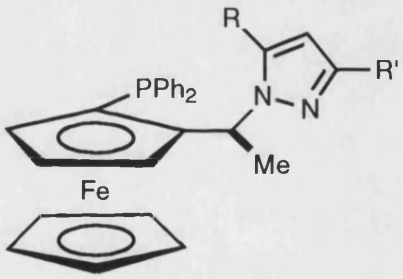
Pfaltz and Helmchen have also applied their oxazoline-phosphine ligands to the amination of meso, allyl systems using a variety of nitrogen sources to give a very high degree of enantioselectivity in some cases (see scheme 2.14).[106]

Scheme 2.14:



Perhaps the most impressive example of enantioselective allylic amination is that reported by Togni.[107] Amination of meso, allyl systems with benzylamine in the presence of ferrocenyl pyrrazole ligands has resulted in the formation of aminated products in up to 99% enantiomeric excess (see fig. 2.9).

Fig. 2.9:



SECTION 2:

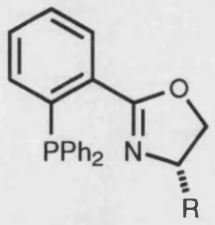
CHAPTER 2: SYNTHETIC STRATEGY FOR DIAZAPHOSPHOLIDINE LIGANDS AND THEIR APPLICATION IN AMINO ACID SYNTHESIS

General Structure of the Proposed Diazaphospholidine Ligands

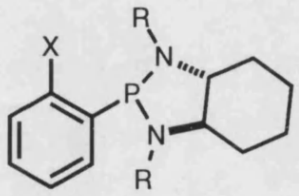
By analogy with the oxazoline-phosphine ligands developed by Pfaltz, Helmchen and Williams the proposed diazaphospholidine ligands were designed to incorporate both a phosphine and hetero-group capable of coordinating to palladium in a bidentate fashion (see fig. 2.10).[93]

Fig. 2.10:

Pfaltz, Helmchen and Williams



Chiral Diazaphospholidine

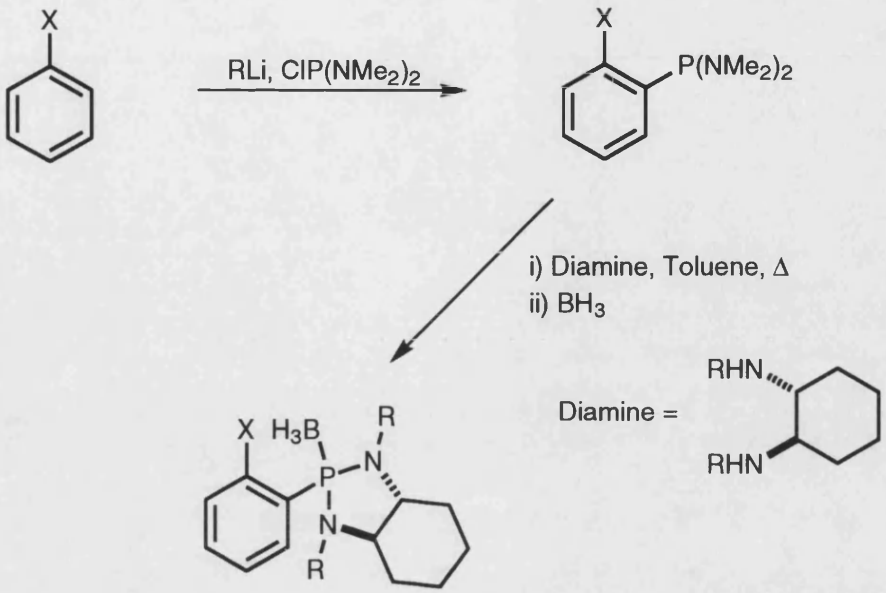


It was envisaged that a variety of ligands based on this general structure could be synthesised by simple variation of the hetero-group X (e.g.. OMe, NMe_2, OR) and by variation of the R groups on nitrogen (e.g.. Me, iPr, Bn). Initial studies would focus on use of the C_2-symmetric *trans*- (R,R)-1,2-diamino cyclohexane to create a chiral environment close to the phosphorus atom but in principle any C_2-symmetric diamine could be used to this effect.

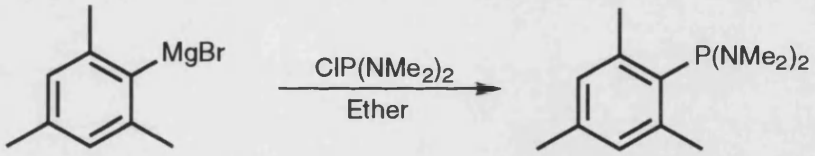
Synthesis of the ligands as their phosphorus-borane complexes could hopefully be achieved by introduction of a bis-aminophosphine *ortho* to the hetero-group X and subsequent reaction with a diamine followed by addition of a borane source (see scheme 2.15).

Buono has reported the reaction of various aryl Grignard reagents with chloro-bis(dimethylamino)-phosphine to give the corresponding bis-aminophosphines in good yield (see scheme 2.16).[10, 108] It was thus reasonable to assume that an analogous reaction with aryllithiums, generated by an *ortho* lithiation procedure (using the *ortho* directing ability of X), would result in formation of the desired bis-aminophosphine intermediates.[35]

Scheme 2.15:

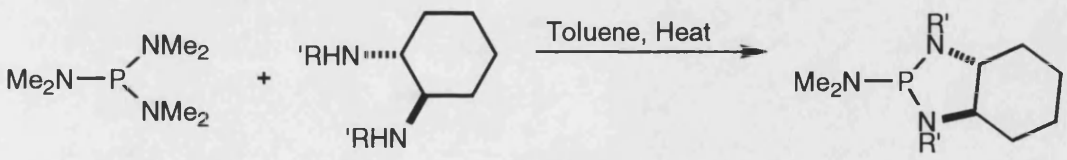


Scheme 2.16:



Whilst the reaction of bis-aminophosphines with amino alcohols has some considerable literature precedent the analogous reaction with diamines has only been carried out using HMPT (see scheme 2.17).[1, 8] The reaction with amino alcohols was carried out by Richter in 1984 when he reacted a variety of bis-aminophosphines with prolinol to give oxazaphospholidines with reasonable diastereoselectivity (see scheme 2.18).[9] It was hoped that the use of C_2-symmetric diamines in this reaction would result in the formation of enantiomerically pure diazaphospholidines. Indeed the use of C_2-symmetric diamines would give products which were not chiral at phosphorous and thus the need to separate diastereomers would be obviated.

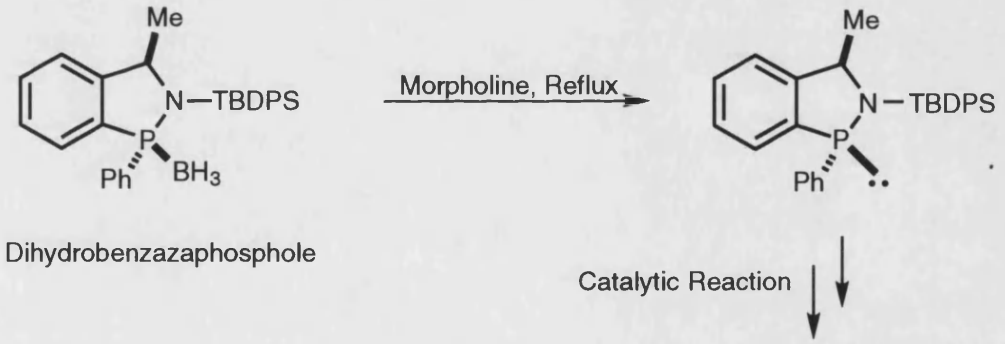
Scheme 2.17:



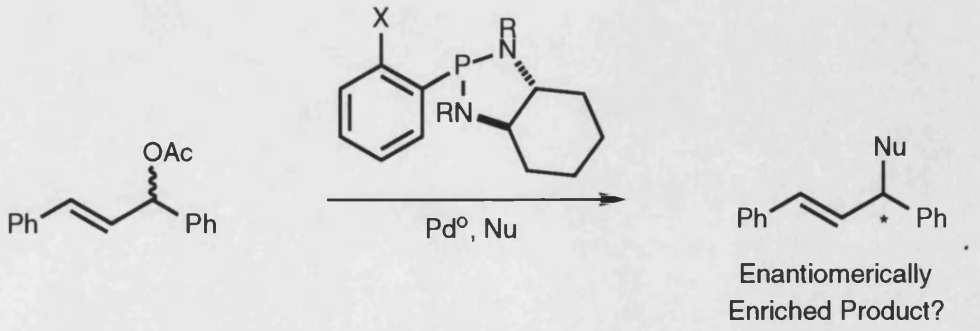
Scheme 2.18:

It was hoped that *in situ* protection of the diazaphospholidine ligands with borane would aid in their isolation and subsequent purification. Literature precedent and previous experience within the Wills group has demonstrated that many phosphines and aminophosphines can be successfully protected as borane complexes resulting in the formation of highly crystalline materials (see scheme 2.19).[86, 109] It has also been demonstrated that the borane group can be removed *in situ* prior to use of the ligand in transition metal catalysed reactions.[86] Treatment of borane complexes with amines (e.g. morpholine and DABCO) under reflux has provided an efficient means of borane removal and it was hoped that such a procedure could be successfully applied to the proposed diazaphospholidine ligands immediately prior to their use in catalytic reactions.

Scheme 2.19:



Scheme 2.20:



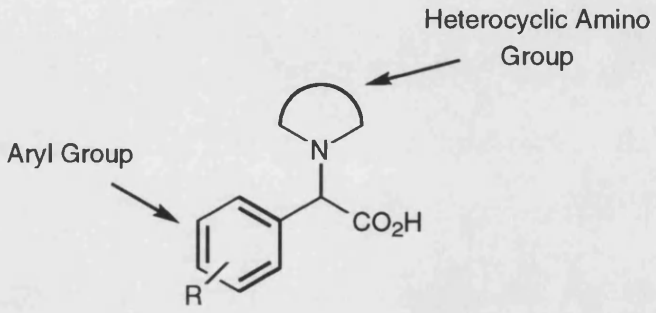
Once the synthesis of the diazaphospholidine ligands had been achieved it was proposed that they should be employed in the palladium catalysed substitution of 1,3-diphenyl-3-acetoxy-

1-propene as a means of comparison with the related ligands of Pfaltz, Helmchen and Williams (see scheme 2.20).[93]

Asymmetric Synthesis of Novel Amino Acids

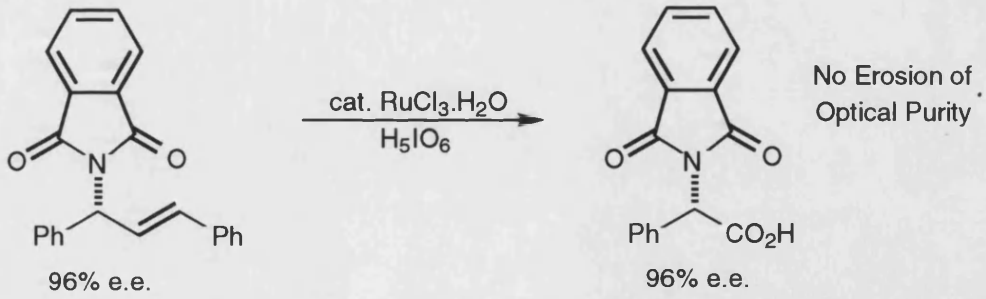
A possible application of the allylic amination reaction was envisaged to be the preparation of novel, α-aryl amino acids possessing N-heterocyclic units (see fig. 2.11).

Fig. 2.11:



Williams has recently reported the conversion of N-protected allylic amines to amino acids *via* an oxidative cleavage of the allylic double bond to give an acid.[110] This was accomplished using the ruthenium catalysed, periodic acid method developed by Sharpless and co-workers, which was found to give the desired acid with no significant erosion of optical purity (see scheme 2.21).[111]

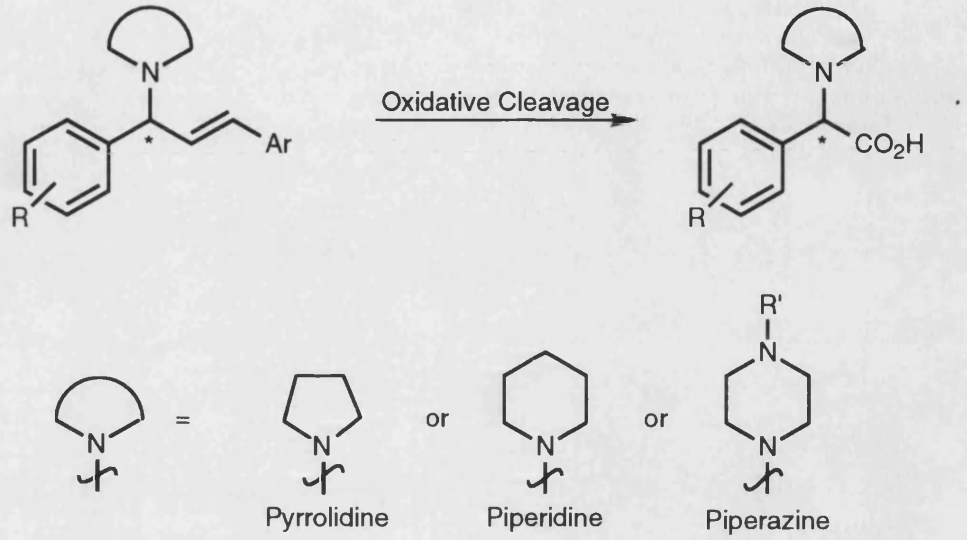
Scheme 2.21:



Our goal was to utilise this methodology to enable the synthesis of novel amino acids where the α-aryl group could derive from a 1,3-diaryl allyl system with the possibility of introducing electronically and sterically diverse aryl substituents. We also planned to investigate the use of cyclic, secondary, amines in the allylic amination to ultimately yield amino acids with heterocyclic amino groups. Use of an N-protected piperazine in this manner could also allow for the possibility of further manipulation of the second heterocyclic amino group enabling the synthesis of more complex amino acids (see scheme 2.22).

With this in mind initial investigations would involve the allylic amination of the 1,3-diphenyl allyl system with heterocyclic amines (pyrrolidine, piperidine etc.) in the presence of a diazaphospholidine ligand.

Scheme 2.22:



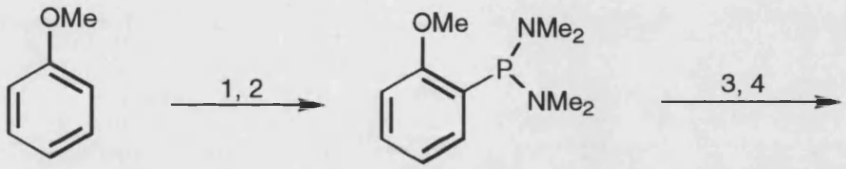
SECTION 2:

CHAPTER 3: RESULTS AND DISCUSSION

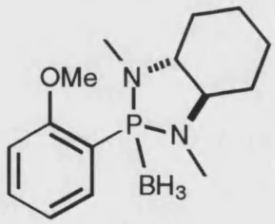
Preparation of the Proposed Diazaphospholidine Ligands

Synthesis of the borane protected ligand (**32**) could be achieved in two steps starting from anisole (see scheme 2.23). Lithiation of anisole using 1 equivalent of n-BuLi in THF at room temperature, for 3hrs, followed by quenching with chloro (bis-dimethylamino) phosphine[108] at -78°C gave o-anisyl (bis-dimethylamino) phosphine (**31a**) in 50% yield, after fractional distillation.[11] Reaction of (**31a**) with (R,R)-*trans*-N,N'-dimethyl-1,2-diamino cyclohexane (**17**) in refluxing toluene for 2 days, followed by addition of BMS gave the desired borane complex (**32**) in 50% yield, after purification by flash chromatography. (**32**) was recrystallised from an ethyl acetate-hexane mixture to give plate-like crystals suitable for X-ray analysis (see Appendix Chapter 4).

Scheme 2.23:



(**31a**) 50%



(**32**) 50%

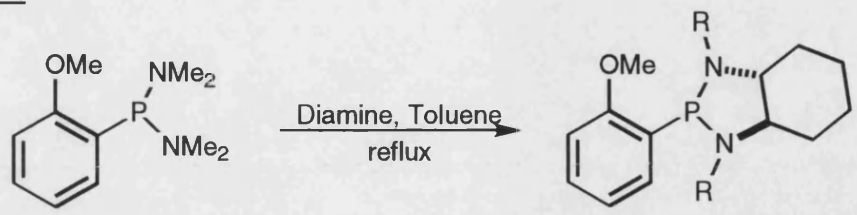
1) n-BuLi, THF, rt. 3hrs; 2) $ClP(NMe_2)_2$, THF;
3) diamine (**17**), toluene, reflux; 4) BMS

Whilst protection of the desired ligand (**33a**), as the P-BH_3 complex (**32**), aided considerably in its purification, removal of the borane unit prior to use in palladium catalysed reactions proved to be a problem. Use of the standard method for borane removal (heating the complex in the presence of excess morpholine[86]) resulted in decomposition and no ligand-palladium complex could be formed. Instead the instant formation of a thick, black precipitate was observed on addition of the palladium source.

As a result it was decided that direct preparation of the unprotected diazaphospholidine (**33a**) should be attempted. Reaction of (**31a**) with diamine (**17**) in refluxing toluene for 3 days gave ligand (**33a**) as a pale cream, waxy, solid in quantitative yield. Encouraged by this result, synthesis of related ligands (**33b**), R = iPr and (**33c**), R = Bn, from the

corresponding diamines was attempted using the same procedure as for (**33a**) (see scheme 2.24 and table 2.2).[1, 77]

Scheme 2.24:



(**31a**)

(**33a**) R = Me 100%
(**33b**) R = iPr 0%
(**33c**) R = Bn 100%

Table 2.2:

Compound	R	Time (days)	Yield (%)
33a	Me	3	100
33b	iPr	3	-
33c	Bn	6	100

Even after refluxing for 3 days none of the expected (**33b**) could be detected, in fact NMR analysis of the solution showed a 1:1 mixture of starting materials. Evidently the N-iPr groups created too much steric hindrance around the nitrogen atoms and the desired reaction could not occur. This was not the case for ligand (**33c**) which could be formed in quantitative yield if the reaction was allowed to continue for an extra 3 days.

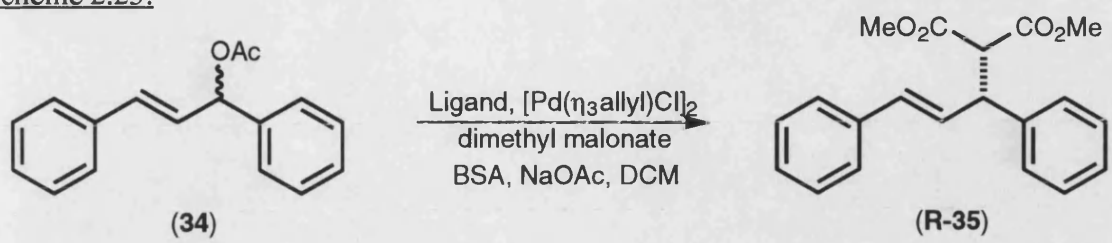
Application of ligands (**33a**) and (**33c**) to Palladium Catalysed Allylic Alkylations

A good test of the diazaphospholidine ligands' ability to induce asymmetry was considered to be the palladium catalysed allylic alkylation reaction. This reaction has been studied extensively in recent years and is generally believed to be a good method for testing new chiral phosphine ligands (see Section 2, Chapter 1).

The specific example chosen in this case, was the substitution of the allylic substrate 1,3-diphenyl-3-acetoxy-1-propene (**34**) with dimethyl malonate (see scheme 2.25). The specific reagents used in this reaction were chosen for a number of reasons. Firstly palladium allyl chloride dimer was employed as the palladium source because it has been shown to be a good source of Pd^0 for this type of substitution reaction.[86, 93, 94] The use of N,O-bis trimethylsilyl acetamide (BSA) as base to deprotonate dimethyl malonate instead of the sodium salt of dimethyl malonate was chosen because good results had been achieved using this method in previous work carried out by the Wills group.[86, 112] Finally a small amount

of sodium acetate was added to the reaction as a catalytic base to activate the BSA and to enhance the dynamic kinetic resolution of racemic acetate (**34**) and thus boost the yields of the alkylation reaction (see Section 2, Chapter 1).[113]

Scheme 2.25:



(34) (R-35)

When 20mol% of ligand (**33a**) and 5mol% of palladium allyl chloride dimer (i.e. 10mol% of Pd) were used in the alkylation reaction a 97% yield, of the desired alkylated product (**35**), was achieved after stirring for 16hrs at room temperature. The enantiomeric excess of the product was determined to be 89% (R) using the (+)-Eu(hfc)$_3$ chiral shift reagent (see table 2.3).[86]

Encouraged by this very promising result, ligand (**33c**) was then applied to the same alkylation reaction keeping all other conditions constant. It had been hoped that the increased steric bulk of the N substituents (Bn as opposed to Me) would induce even greater enantioselectivity in the reaction. Unfortunately this increased bulk served to slow the reaction down and in fact slightly decreased the enantioselectivity. Product (**35**) was isolated in 48% yield and the enantiomeric excess was determined to be only 64% (R) in this case.

Table 2.3:

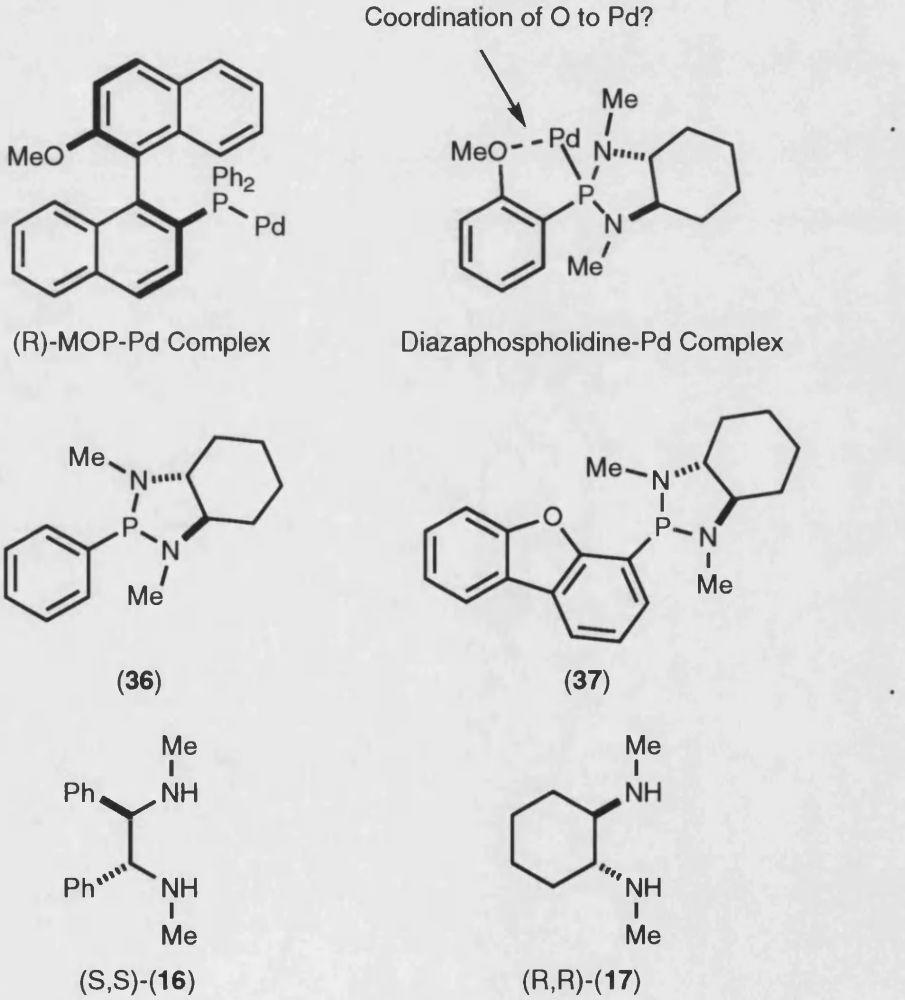
Ligand	mol% L	mol% Pd	Time	Yield (**35**) %	e.e. %
33a	20	10	16	97	89 (R)
33c	20	10	24	48	64 (R)
36	20	10	16	97	28 (S)
37	20	10	19	92	35 (R)
15	20	10	19	6	15 (S)

Exploration of the Factors Affecting Enantioselectivity

From the above results it was thought likely that the steric nature of the nitrogen substituent was playing an important role in the enantioselection induced by the diazaphospholidine ligands. However in order to postulate a model to explain this stereoinduction more information about the nature of the active Pd-ligand complex was required.

It seemed reasonable to assume that the diazaphospholidine ligand was coordinated to palladium *via* the phosphorus atom but involvement of the ether oxygen in formation of the ligand-palladium complex could not be assumed. Hayashi and co-workers have reported an example of a ligand-palladium complex where the ligand (MOP a derivative of BINAP) possesses both a phosphine and a methyl ether which are in theory both capable of coordinating to palladium.[114] Contrary to expectation, the major species present in solution and solid phase (as determined by NMR and X-ray analysis respectively) was found to exhibit coordination to palladium only *via* the phosphorus atom, in a mono dentate fashion. In order to test whether the ether oxygen of ligand (**33a**) was involved in coordination, ligand (**36**) (where the *o*-anisole was replaced by a phenyl group) was synthesised and tested in the alkylation reaction (see fig. 2.12).

Fig. 2.12:



Ligand (**36**) was synthesised in quantitative yield from phenyl (bis-dimethylamino) phosphine[9] and diamine (**17**) under the same conditions as those used to prepare ligand (**33a**). When ligand (**36**) was employed in the alkylation reaction the alkylated product (**35**) was isolated in 97% yield, similar to the case for (**33a**). However the enantiomeric excess was determined to be 28% in favour of the (S) configuration, as opposed to (R) for ligands

(**33a**) and (**33c**) (see table 2.3). From this result it seemed evident that the ether oxygen in ligands (**33a**) and (**33c**) was playing an important role in the formation of a conformationally rigid, bidentate, palladium complex leading to the production of (**35**) with a high degree of stereoselectivity. The absence of a second coordination site in ligand (**36**) meant that no single, conformationally restricted palladium complex could form allowing the alkylation reaction to proceed with little control over enantioselectivity.

The effect of the steric demand of the ether substituent on the enantioselectivity, of the alkylation reaction, was briefly investigated by synthesis of the dibenzofuran derived ligand (**37**) (see fig. 2.12). This ligand was synthesised from dibenzofuran-bis (dimethylamino) phosphine (**31b**), in a similar manner to that described for ligand (**33a**). Application of this ligand to the allylic alkylation reaction gave (**35**) in a respectable 92% yield. The enantiomeric excess was determined to be 35% again in favour of the (R) isomer. It seems reasonable to conclude that whilst ligand (**37**) probably operated *via* a similar mechanism to (**33a**), the increased bulk adjacent to the ether group had a deleterious effect on the degree of enantioselectivity achieved during the reaction. Unfortunately time did not allow for an extensive investigation into the effect of changing the nature of this coordinating group more dramatically, for example using nitrogen or sulfur derivatives.

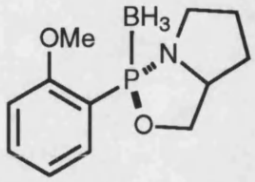
One final, important, consideration had to be made before a model for the stereoinduction could be proposed. Lemaire has recently reported the use of (S,S)-*trans*-N,N'-dimethyl-1,2-diphenyl ethylene diamine (**16**) as an extremely effective ligand for the palladium catalysed allylic alkylation reaction, giving enantioselectivities of up to 95%.[115] The possibility that the diazaphospholidine ligands could be decomposing to liberate diamine (**17**) in the course of the alkylation reaction had to be addressed. Use of diamine (**17**) as ligand in the alkylation reaction gave only a 6% yield of (**35**) with an enantiomeric excess of 15% (S). Clearly, even if some diamine was liberated during the alkylation reaction using the diazaphospholidine ligand (**33a**) this could not account for the high levels of enantioselectivity previously achieved in the alkylation reactions.

Model for the Mechanism of Stereoinduction Using Ligand (33a)

X-ray data for analogous diazaphospholidine oxides clearly shows that the ring nitrogen atoms are significantly distorted from planarity and that the geometry of the exocyclic nitrogen substituents is controlled by the stereochemistry of the 5,6-ring junction. (This was discussed in some detail in Chapter 4 of Section 1). It seems likely that this phenomenon would also control the conformation of the exocyclic nitrogen substituents in diazaphospholidine (**33a**). Indeed an X-ray structure of oxazaphospholidine P-BH_3 complex (**38**) derived from prolinol, also shows the ring nitrogen geometry to be midway between planar and tetrahedral (ΣN = 341.6°) (see fig. 2.13).[116] X-ray analysis of the

diazaphospholidine P-BH_3 complex (**32**), was carried out to determine the nitrogen geometry for this case.

Fig. 2.13:

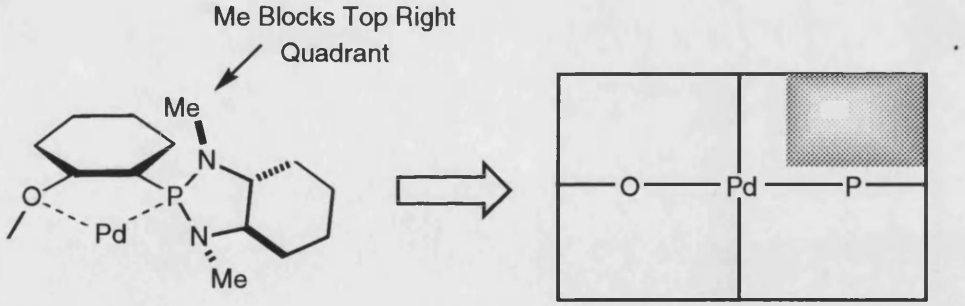


(**38**)

The X-ray structure of (32) (see Appendix Chapter 4) clearly showed that the nitrogen geometry was midway between planar and tetrahedral. The ΣN values were calculated to be 343.7 and 342.2° for N17 and N9 respectively, giving rise to an out of plane shift of approximately 0.36Å. Also evident from the structure was the geometry on the N-Me substituents which were clearly opposed to the adjacent ring CH_2 groups as expected. The position of the borane group demonstrated that the phosphorus was tetrahedral and gave an approximate position for the lone pair in the unprotected diazaphospholidine.

Taking into account the ground state conformation of the ligand, as determined by X-ray analysis, and the fact that palladium coordination to the ether oxygen in ligand (33a) seemed to be a requirement for high levels of stereoinduction in the allylic alkylation reaction, the following model was proposed (see fig. 2.14).

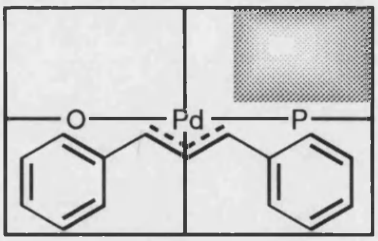
Fig. 2.14:



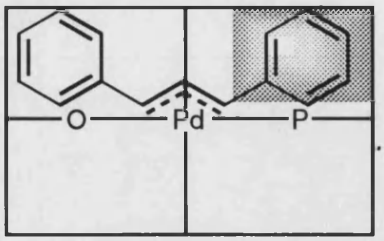
The steric effect of the upper N-Me group serves to block the top right hand quadrant in the palladium-ligand complex. Subsequent coordination of the 1,3-diphenyl allyl group could then occur in two ways, either in a "W" or "M" conformation (see fig. 2.15).

If coordination occurred *via* the "W" conformation then one of the phenyl groups, of the allyl species, would extend into the top right-hand quadrant and hence be subject to an unfavourable steric interaction. No such interaction would occur if coordination was *via* the "M" conformation and thus this would be expected to be favoured.

Fig. 2.15:



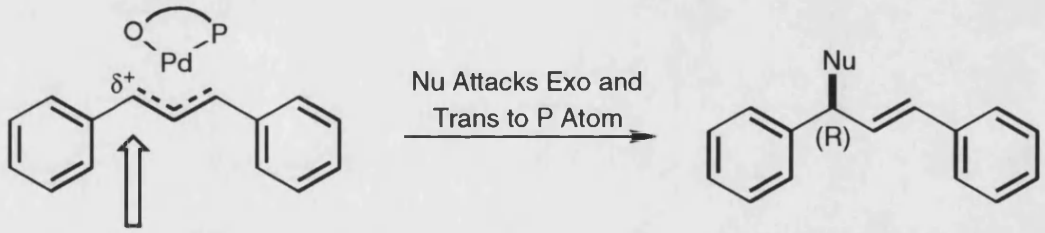
M Conformation
No Bad Steric Interactions



W Conformation
Steric Clash in Top Right Quadrant

Attack of the nucleophile would then be expected to occur on the *exo* face of the coordinated allyl unit and at the end of the allyl *trans* to the phosphorus atom. This is due to a greater *trans* labilising effect induced by the phosphorus ligand which is well precedented in literature examples (see discussion in Section 2 Chapter 1). Attack of the nucleophile in this manner would lead to the formation of the (R) enantiomer of the alkylated product (**35**) which was indeed the outcome observed when ligand (**33a**) was employed in the substitution reaction (see scheme 2.26).

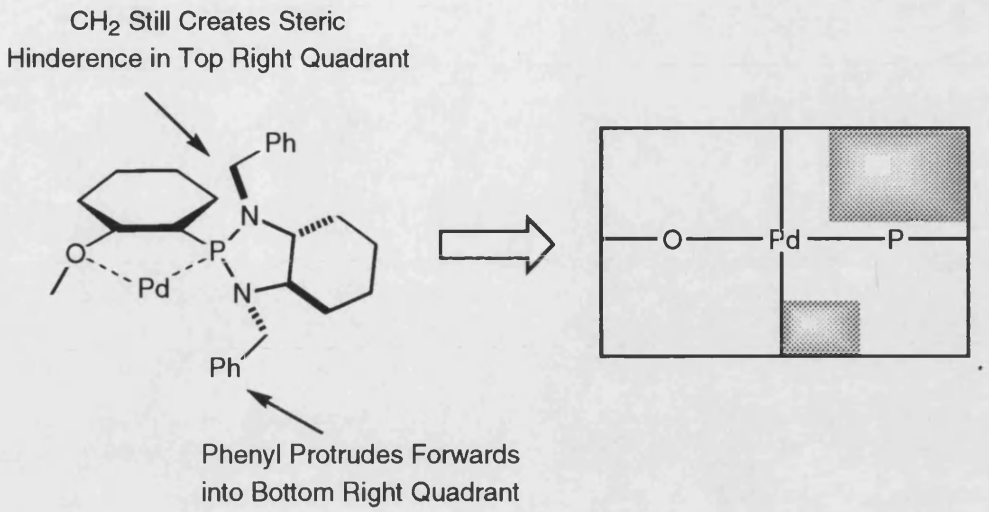
Scheme 2.26:



Observed Major Isomer

In the case of ligand (**33c**) a similar model could be proposed (see fig. 2.16). The reason for the reduced enantioselectivity induced by this ligand then became clear. The benzylic CH_2 of the upper nitrogen still serves to block the top right-hand quadrant, but an extra steric effect is also produced by the phenyl group, of the lower nitrogen substituent, protruding into the bottom right-hand quadrant to some extent. Now there is a steric impediment to the coordination of the 1,3-diphenyl allyl unit in both the "M" and "W" conformations. The fact that a selectivity of 64% in favour of the (R) isomer of product (**35**) was still observed, demonstrated that the steric effect caused by the upper CH_2 group was still the major one.

Fig. 2.16:



Optimisation of the Allylic Alkylation Using Ligand (**33a**)

Having established that ligand (**33a**) produced the greatest levels of enantioselectivity, out of those ligands investigated so far, it was decided that reaction conditions for the alkylation procedure should be optimised for this ligand (see scheme 2.27 and table 2.4).

Firstly the ligand to palladium ratio was varied to assess whether a 2:1 ratio was essential to maintain the rate and stereoselectivity of the reaction. (Generally a 2:1 ratio has been used in literature examples[86, 93, 94]). Use of a 1:1 ratio of ligand to palladium in the allylic alkylation reaction was observed to give a slightly impaired rate of alkylation and a minimal reduction in enantioselectivity to 83% (R), compared to 89% (R) when a 2:1 ratio was employed. This slight loss of enantioselectivity was probably caused by a reduction in the effective concentration of the active ligand-palladium complex present in solution, it was thus decided that a ligand to palladium ratio of 2:1 should be maintained in future reactions.

Next consideration was given to the palladium loading used in the alkylation reaction. Environmental and economic factors dictated that as little palladium as possible should be used in the reaction, but enough should be present to maintain the desired high levels of enantioselectivity. Reduction of the palladium loading to 5mol% gave almost identical results (88% e.e) to those obtained when 10mol% was employed, however a further reduction to 2mol% resulted in an appreciable reduction in selectivity (82% e.e). Clearly the use of no lower than 5mol% of palladium would be appropriate to enable the high levels of enantioselectivity to be maintained in future reactions.

Finally the effect of temperature was investigated. It was considered possible that a reduction in temperature might cause a slight enhancement in the selectivity of the reaction. When the

alkylation reaction was carried out at 0°C product (**35**) was produced in 89% e.e.. The only difference observed was a slight reduction in the rate of reaction, which was to be expected.

So, in conclusion, the optimum conditions for the allylic alkylation were; using a 2:1 ligand to palladium ratio, at a palladium loading of 5mol%, and stirring at room temperature. These conditions were found to be in accordance with the conditions employed in other similar reactions cited in the literature.[86, 93, 94]

Scheme 2.27:

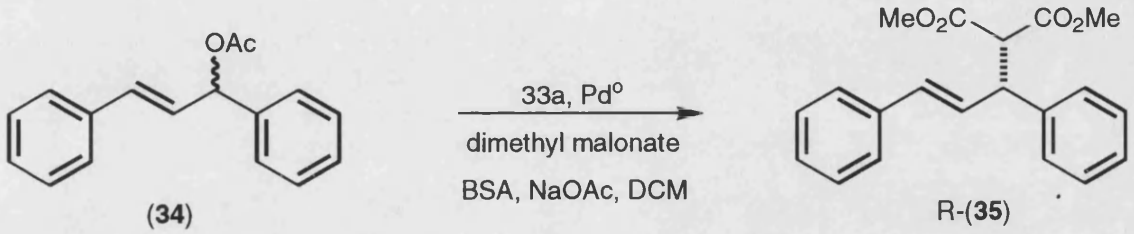


Table 2.4:

mol% (**33a**)	mol% Pd	Temp. (°C)	Time (hrs)	Yield (%)	e.e (%)
20	10	20	16	97	89 (R)
10	10	20	20	89	83 (R)
10	5	20	12	85	88 (R)
4	2	20	20	94	82 (R)
20	10	0	7	68	89 (R)

Application of Ligand (**33a**) in Allylic Amination Reactions

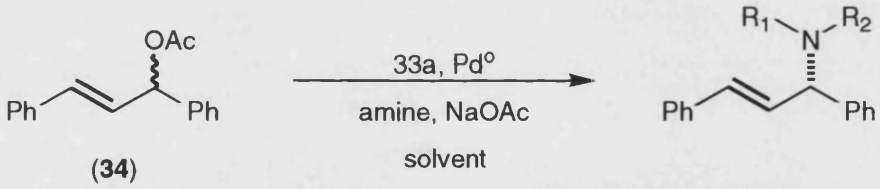
Whilst the allylic alkylation reaction had provided a good means for testing the applicability of the diazaphospholidine ligands to allylic substitution reactions, its synthetic utility was however rather limited. Our interest in the asymmetric synthesis of amino acids lead us to investigate the analogous allylic amination reaction (see scheme 2.28). Products formed in the amination of the 1,3-diphenyl allyl system have been successfully converted into amino acid derivatives (see Section 2 Chapter 2) and we hoped to utilise this methodology in the synthesis of novel amino acid derivatives.

Literature precedent indicated that benzylamine was a good nucleophile in the allylic amination reaction, in some cases giving aminated products with a high degree of enantioselectivity.[106] The use of benzylamine as nucleophile in the amination of 1,3-diphenyl-3-acetoxy-1-propene (**34**) in the presence of catalytic amounts of ligand (**33a**), palladium allyl chloride dimer and sodium acetate in a DCM solution at room temperature

gave the desired amine (**39**)[106] in 68% yield after stirring for 42hrs (see scheme 2.28 and table 2.5). The enantiomeric excess was determined to be 78% (S) by chiral HPLC analysis using a Chiralcel OD column. (The sample was determined to be enriched with the (S) isomer by comparison of the sign of the optical rotation and retention time measured by HPLC with literature examples[106]). Although the amination reaction proceeded at a reduced rate compared to the analogous alkylation reaction a high degree of stereoinduction, in the same sense, was still occurring presumably *via* the same mechanism.

Comparison with literature procedures for the allylic amination reaction lead to attempts to improve the rate of amination by, employing THF as the solvent instead of DCM and looking at the effect of elevated temperature upon the reaction rate.[106, 107] The use of THF as solvent did serve to improve the rate of reaction to some extent, giving amine (**39**) in 49% yield after 20hrs, but with a slight drop in enantioselectivity to 73% (see entry 2 in table 2.5). When the amination was carried out in THF at 50°C a dramatic improvement in the rate was observed giving amine (**39**) 77% yield after only 5hrs but this was also accompanied by an unacceptable 10% drop in enantiomeric excess (see entry 3 table 2.5).

Scheme 2.28:



(**34**)

R_1 = H, R_2 = Bn (**39**)
R_1 = H, R_2 = R-(+)-α-methyl benzyl (**41**)
R_1 = H, R_2 =S-(-)-α-methyl benzyl ent-(**41**)
R_1 = H, R_2 = tosyl (**43**)
R_1 = R_2 =-C_4H_8- (**45**)
R_1 = R_2 =-C_2H_4-N-(Bn)-C_2H_4- (**47**)

In order to assess whether there would be any effect of a chiral centre within the nucleophile on the enantioselectivity of the amination reaction the use of α-methyl benzylamine (**40**) as a nucleophile was investigated (in some cases the use of a chiral nucleophile has resulted in the formation of enantiomerically enriched products, see Section 2 Chapter 1). (R)-(+)-(**40**) gave aminated product (**41**) in 67% yield after stirring at room temperature in DCM for 168hrs. The diastereomeric excess was measured by NMR analysis to be 78% in favour of the (S)(R) isomer.

Table 2.5:

Entry	Nu	Product	Solvent	Temp °C	Time hrs	Yield %	e.e. %
1	$BnNH_2$	**39**	DCM	20	42	68	78 (S)
2	$BnNH_2$	**39**	THF	20	20	49	73 (S)
3	$BnNH_2$	**39**	THF	50	5	77	68 (S)
4	(R)-(+)-**40**	**41**	DCM	20	168	67	78 (S)(R)
5	(R)-(+)-**40**	**41**	THF	50	8	51	61 (S)(R)
6	(S)-(-)-**40**	**ent-41**	THF	50	8	67	61 (S)(S)
7	**42**	**43**	DCM	20	64	45	76 (S)
8	**44**	**45**	DCM	20	41	48	68 (S)
9	**46**	**47**	DCM	20	16	63	58 (S)

The possibility of match-mismatch effects of chirality present in the ligand and the chiral amine was investigated by setting up two parallel reactions using both the (R)-(+) and (S)-(-)-isomers of α-methyl benzylamine (**40**) under identical reaction conditions. Stirring for 8hrs in THF at 50°C gave amine (**41**) in 51% yield and 61% d.e. compared to (**ent-41**) which was produced in 67% yield and 61% d.e.. Clearly the chiral centre present in the nucleophile was having no effect on the enantioselectivity of the amination reaction.

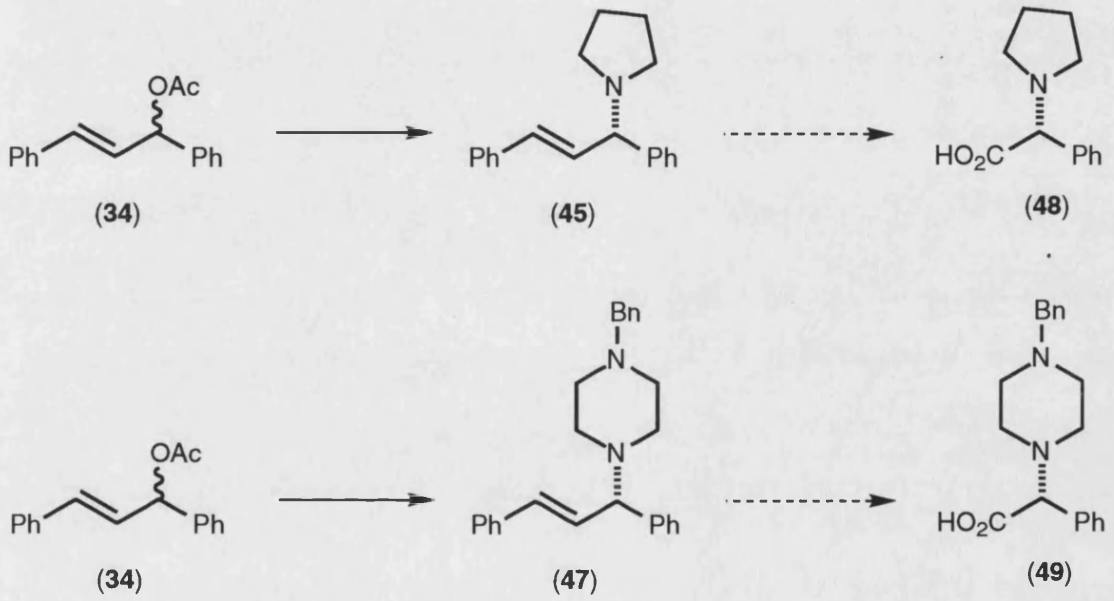
From the results obtained thus far it was clear that the best enantioselectivities for the amination reaction were achieved by using DCM as solvent at room temperature. It was decided that the sluggish rate of the reaction under these conditions could be tolerated so long as the enantioselectivity of the reaction remained at reasonable levels.

The allylic amination procedure was then extended to the use of other nitrogen sources as nucleophiles. The sodium salt of tosylamide (**42**) had been demonstrated, by Pfaltz and co-workers using their oxazoline-phosphine ligand, to give a higher degree of enantioselectivity in the substitution of the allylic substrate (**34**) when compared to the result obtained for benzylamine.[106] The application of (**42**) as nucleophile in the substitution of (**34**) using diazaphospholidine ligand (**33a**) (see entry 7 in table 2.5) gave the desired allyl sulfonamide (**43**) in a reasonable 45% yield but with a disappointing enantiomeric excess of 76%, no better than the case for benzylamine under analogous conditions.

Allylic Amination Using Cyclic Secondary Amines: Towards the Synthesis of Novel Amino Acids

As discussed in Section 2 Chapter 2, the use of cyclic, secondary amines as nucleophiles in the palladium catalysed allylic amination reaction has not been greatly explored. The use of amines such as pyrrolidine (**44**) and N-benzyl piperazine (**46**) as nucleophiles in the allylic amination of substrate (**34**) could in theory lead to the synthesis of amino acids (**48**) and (**49**) as illustrated below (see scheme 2.29).

Scheme 2.29:



When pyrrolidine (**44**) was employed as the nucleophile in the allylic amination of (**34**) (see entry 8 in table 2.5) using ligand (**33a**), the desired allylic amine (**45**) was produced in 48% yield, as a highly crystalline solid. The enantiomeric excess was measured by HPLC analysis to be 68% in favour of the (S)-isomer (determined to be (S) by analogy with the other results obtained using ligand (**33a**) and by the sign of the optical rotation). Similarly N-benzyl piperazine (**46**) yielded 63% of the crystalline, allylic amine (**47**) with a selectivity of 58% e.e. in favour of the (S)-isomer, again determined by HPLC analysis. The lower level of enantioselectivity achieved in this case was a little disappointing, but owing to the highly crystalline nature of the product could in theory be improved by using fractional crystallisation techniques.

Unfortunately time did not allow for the conversion of the allylic amines (**45**) and (**47**) into their respective amino acids (**48**) and (**49**). This work and the application of the amination methodology to other substrates is the subject of an ongoing study within the Wills group.

General Conclusions

CONCLUSIONS AND FUTURE WORK:

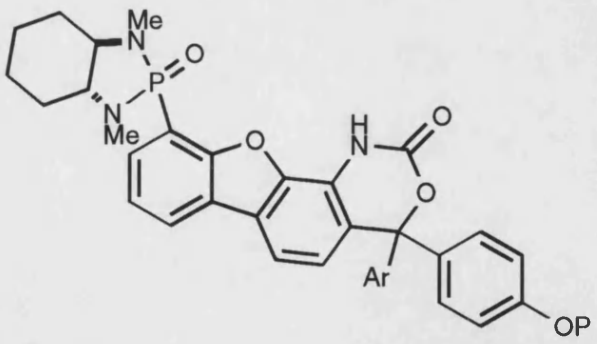
P(V)-Diazaphospholidine Oxides

This part of the project resulted in the successful synthesis of two chiral diazaphospholidine oxide derived cleft receptors (**24**) and (**25**). It was demonstrated that both of these receptors are capable of binding to N-t-Boc protected amino acids with binding constants in the region of $10^3 M^{-1}$. Furthermore receptor (**24**) was capable of enantioselective binding to alanine derivatives with an e.e. of 40%.

Initial attempts at applying these cleft receptors to the asymmetric synthesis of amino acid derivatives were unsuccessful. Clearly much more work has to be done to understand the nature of the proposed catalytic cycle and develop a method which would enable asymmetric catalysis to be a possibility.

Perhaps a more suitable application of the cleft receptors would be as a chiral stationary phase for HPLC analysis of amino acid derivatives. In order to achieve this a means of anchoring the clefts to a solid support, such as silica, would have to be devised. One possibility would be to modify the clefts to include a point of attachment (e.g. an ether linkage) at one or both of the phenyl rings in the cyclic urethane unit (see fig. 3.1).

Fig. 3.1:



Such a derivatisation could be achieved early on in the synthesis by employing a *para* substituted benzophenone as the electrophile in the second lithiation reaction (P = a suitable protecting group). Once the receptor synthesis had been completed this *para* substituent could then be deprotected and attached to the solid support.

P(III)-Diazaphospholidines

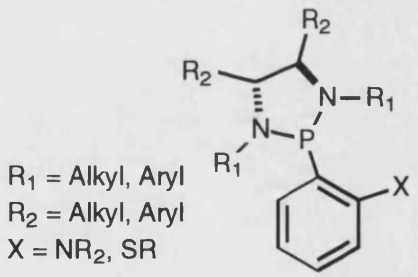
A range of diazaphospholidines have been synthesised and successfully employed as ligands for palladium in allylic substitution reactions. The anisole derived ligand (**33a**) was found to

give a high level of enantioselectivity (58-89% e.e.) in both the allylic alkylation and amination of the 1,3-diphenyl allyl system using a range of substrates.

Perhaps the most interesting results were achieved when the amination was carried out using cyclic secondary amines as nucleophiles. The enantiomerically enriched products could potentially be converted into novel amino acid derivatives via an oxidative cleavage of the allylic double bond.

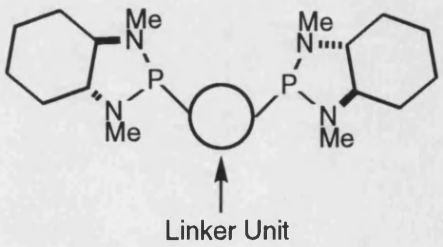
Although the results presented showed a good degree of enantioselectivity there is much room for improvement if this family of ligands is to compete with other literature examples in analogous palladium catalysed reactions. There are two main ways in which the ligand could be modified: firstly a different heteroatom could be employed instead of the anisole oxygen, both amino and thio derivatives could be readily synthesised from commercially available materials; secondly the chiral diamine could be changed in order to alter the chiral environment surrounding the phosphorus centre (see fig. 3.2).

Fig. 3.2:



A further possibility would be to synthesise a dimeric diazaphospholidine (see fig. 3.3), joined by an aromatic or aliphatic linker unit, which would be able to operate as a bidentate phosphine ligand and coordinate to other transition metal such as ruthenium and rhodium. This would open the door to the application of diazaphospholidines in other transition metal catalysed reactions such as asymmetric hydrogenation, hydroformylation, Heck reactions and many more.

Fig. 3.3:



Experimental

EXPERIMENTAL: GENERAL

SOLVENTS

THF and ether were distilled from their corresponding sodium benzophenone ketals.
Toluene was distilled from sodium.
DCM was distilled from calcium hydride.
Methanol was distilled from activated magnesium sulfate
DMF was distilled under reduced pressure (water aspirator) from anhydrous magnesium sulfate and stored over 4Å molecular sieves.
All other solvents were used as supplied unless otherwise stated.
Petrol refers to petroleum ether with a boiling range of 60-80°C.

TEMPERATURE CONTROL

Room temperature refers to ambient room temperature normally between 18-22°C.
0°C refers to an ice slush bath.
-78°C refers to an acetone-CO_2 bath.
Heating experiments were carried out using thermostatically controlled oil baths.

REACTION VESSELS

All air and moisture sensitive reactions were carried out in flame or oven dried Schlenk apparatus and under a dry nitrogen or argon atmosphere. Larger scale reactions (>1g) were carried out in two or three necked round bottom flasks fitted with appropriate gas inlet adapters.

CHROMATOGRAPHY

All reactions were monitored using foil or plastic backed commercially available 0.25mm silica gel plates (Merck) and visualised using UV_{254nm} and CAM, PMA, ninhydrin, permanganate or iodine dips as appropriate.

Flash column chromatography was carried out using 60Å silica gel (Merck) unless otherwise stated. All solid products were pre absorbed onto silica, oils were dissolved in a minimal amount of the eluent and pipetted onto the column surface.

Chiral HPLC analyses were carried out on a Waters HPLC system using a Chiralcel OD column.

REAGENTS

Butyllithium Solutions

All butyllithium reagents were stored below 0°C in sealed, water-tight containers. Titration of the solutions against 4-biphenyl methanol in THF at 0°C under inert atmosphere provided an accurate measure of their concentration. Each solution was titrated in such a manner before every use. Aliquots of the butyllithium reagents were measured using oven dried syringes that had been previously purged with nitrogen or argon. Any excess of butyllithium reagent was quenched by washing into dry petrol and slowly adding n-butanol before discarding.

Other Reagents

Most compounds were used as supplied by Aldrich, Fluka or Lancaster. Triethylamine and TMEDA were distilled from calcium hydride and stored over potassium hydroxide pellets under a nitrogen atmosphere. t-Butanol was dried over activated calcium sulfate and distilled under nitrogen before use.

ANALYTICAL TECHNIQUES

Infra-red spectra were recorded as Nujol mulls or chloroform films between sodium chloride plates using a Perkin-Elmer 1310 FTIR spectrophotometer.

NMR spectra were recorded for $CDCl_3$ or DMSO-d6 solutions using a Jeol 270 270MHz, Jeol 400 400MHz, Bruker AC250 250MHz or Bruker ACF400 400MHz spectrometer. All chemical shifts (δ) are measured in ppm down field of tetramethyl silane as internal reference. Coupling constants (J) are measured in Hz. Abbreviations for splitting patterns are as follows: (s) singlet, (bs) broad singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet. DEPT techniques were commonly used to aid interpretation of ^{13}C spectra. ^{31}P spectra were usually fully proton-decoupled for simplicity.

Mass spectra were recorded on a 7070E VG mass spectrometer for all E.I. and C.I. spectra. FAB and HRMS spectra were recorded by the EPSRC Mass Spectrometry service at Swansea.

Microanalysis was performed using a Carlo Erba elemental analyser (MOD 1106).

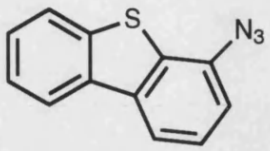
Optical Rotations were recorded using a Perkin-Elmer polarimeter (sodium D line) and a 1cm rotation cell, values for $[\alpha]_D$ are given in 10^{-1}deg cm^2 g^{-1} at the specified temperature.

Single crystal X-ray analyses were carried out as described in the relevant appendices.

EXPERIMENTAL: SECTION 1

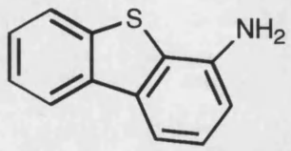
SYNTHESIS OF CYCLIC URETHANES

4-azidodibenzothiophene (**1**)



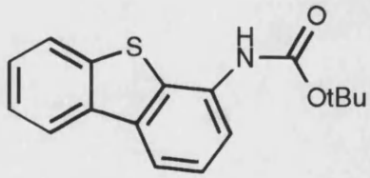
Dibenzothiophene (200mg 1.09mmol) was dissolved in THF (3.0ml) and cooled to -78°C with stirring. n-BuLi (0.87ml, 2.18mmol of a 2.5M solution in hexanes) was added dropwise to give a pale orange solution. The mixture was allowed to warm to room temperature and stirred for 5hrs, during which time the solution became dark red. The solution was recooled to -78°C and a solution of tosyl azide (425mg, 2.18mmol) in THF (2.0ml) was added dropwise. After 2hrs the mixture was allowed to warm to -10°C and stirred for 3hrs. An aqueous solution of sodium pyrophosphate (960mg, 2.16mmol) in water (10ml) was added and the mixture allowed to stir at room temperature over night. The separated aqueous phase was extracted with ether (3 x 10ml), the combined organics were dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The resulting orange solid was purified by flash chromatography on Florisil® (100-200 mesh) eluted with petrol to give the azide (**1**) as a yellow solid (180mg, 74%). $\nu_{max}(CHCl_3$ film)/cm^{-1} 2115 (N_3); δ_H (270MHz; $CDCl_3$) 8.16-8.13 (1H, m), 7.94 (1H, dd, J 7.8, 0.9), 7.89-7.86 (1H, m), 7.53-7.44 (3H, m), 7.25 (1H, dd, J 7.7, 0.9). Due to the instability of this compound the material was carried through to the next stage without further purification.

4-aminodibenzothiophene (**2**)[59]



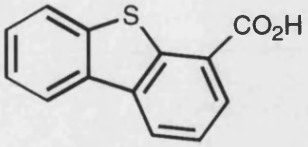
A solution of $SnCl_2.2H_2O$ (270mg, 1.20mmol) in water (2.0ml) and 1,4-dioxane (4.0ml) with stirring at 0°C. 4-Azidodibenzothiophene (**1**) (90mg, 0.40mmol) in 1,4-dioxane (2.0ml) was added dropwise and the mixture stirred at 0°C for 1hr before allowing to warm to room temperature and stirring over night. The mixture was extracted with ethyl acetate (3 x 10ml) and the combined organics dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The brown residue was purified by flash chromatography on silica eluted with a gradient of 10-20% ethyl acetate/petrol to give amine (**2**) as an off-white solid (33mg, 42%). ν_{max}(Nujol)/cm^{-1} 3422, 3313 and 3216 (NH); δ_H (270MHz; DMSO-d6) 8.24-8.21 (1H, m), 8.01-7.98 (1H, m), 7.57 (1H, d, J 7.9), 7.48-7.44 (2H, m), 7.23 (1H, t, J 7.7), 6.75 (1H, d, J 7.7), 5.48 (2H, s, NH_2); δ_C (100MHz; DMSO-d6) 143.2 (C*i*), 138.2 (C*i*), 136.0 (C*i*), 135.9 (C*i*), 126.5 (CH), 125.8 (CH), 124.4 (CH), 123.4 (C*i*), 123.0 (CH), 121.9 (CH), 110.9 (CH), 110.0 (CH); m/z (E.I.) 199 (M^+, 100%), (Found: M^+ 199.0465. $C_{12}H_9NS$ requires M, 199.0455).

Dibenzothiophene-4-tertiarybutoxy carbamate (**3a**)



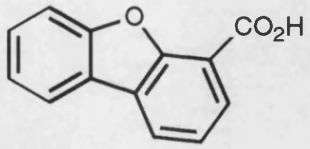
4-Aminodibenzothiophene (**2**) (100mg, 0.50mmol) was dissolved in THF (5.0ml) and cooled to 0°C with stirring. Sodium hydride (20mg, 0.50mmol of a 60% slurry in mineral oil) was added with stirring. After 10min, when the effervescence had stopped, $(Boc)_2O$ (120mg, 0.55mmol) was added and stirred for 30min before allowing to warm to room temperature and stirring further over night. The solvent was evaporated and the residue purified by flash chromatography on silica eluted with a gradient of 1-10% ethyl acetate/petrol to give carbamate (**3a**) as a white solid (52mg, 35%) (see superior route for data).

Dibenzothiophene-4-carboxylic acid (**4a**)[37]



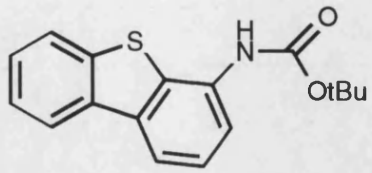
Dibenzothiophene (200mg, 1.09mmol) was dissolved in THF (3.0ml) and cooled to -78°C with stirring. n-BuLi (0.87ml, 2.18mmol of a 2.5M solution in hexanes) was added dropwise to give a pale orange solution. The mixture was allowed to warm to room temperature and stirred for 5hrs, during which time the solution became dark red. The solution was then poured onto a slurry of solid CO_2 in ether (10ml). The excess CO_2 was allowed to evaporate. The resultant yellow precipitate was diluted with ether and 2N NaOH. The aqueous phase was washed with ether and then acidified with 2N HCl until pH 3. The resultant creamy precipitate was extracted into ethyl acetate and the organics dried over sodium sulfate, filtered and solvent removed under reduced pressure. The orange-yellow solid was re-crystallised from hot ethanol to give acid (**4a**) as fine, white crystals (186mg, 75%). (Found: C, 68.5; H, 3.4. $C_{13}H_8O_2S$ requires C, 68.4; H, 3.5%); ν_{max}(Nujol)/cm^{-1} 1667 (C=O); δ_H (270MHz; DMSO-d6) 8.66 (1H, d, J 7.7), 8.44-8.41 (1H, m), 8.17 (1H, dd, J 7.5, 1.1), 8.08-8.04 (1H, m), 7.66 (1H, t, J 7.7), 7.58-7.53 (2H, m); δ_C (100MHz; DMSO-d6) 167.2 (CO_2H), 140.5 (C*i*), 139.9 (C*i*), 136.6 (C*i*), 134.0 (2C*i*), 129.0 (CH), 127.5 (CH), 126.4 (CH), 124.9 (CH), 122.8 (CH), 122.1 (CH); m/z (E.I.) 228 (M^+, 100%), 183 (M^+ - CO_2H, 35).

Dibenzofuran-4-carboxylic acid (**4b**)[36]



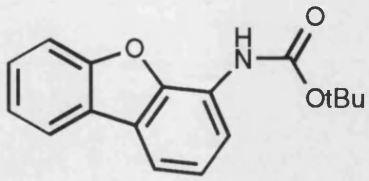
Dibenzofuran (5.0g, 29.7mmol) was dissolved in THF (25.0ml) and cooled to -78°C with stirring. n-BuLi (12.0ml, 29.76mmol of a 2.48M solution in hexanes) was added dropwise with stirring to give an orange/yellow precipitate. After complete addition the mixture was allowed to warm to room temperature and stirred for 3hrs. The orange/brown solution was then cooled to -78°C and poured onto excess CO_2(s) covered with anhydrous ether. The resulting white precipitate was allowed to stand at room temperature for 1hr. The product was extracted into 2N NaOH and the resulting aqueous phase re-acidified with conc. HCl before extracting into ethyl acetate. This organic phase was then dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure to give acid (**4b**) as a white solid (4.67g, 75%). mp. 210-212°C (from EtOH/water) [cf. lit.[36] mp. 213-214°C (from EtOH/water)]; δ_H (270MHz; DMSO-d6) 13.5 (1H, bs, CO_2H), 8.40 (1H, dd, J 7.7, 1.1), 8.20 (1H, d, J 7.7), 8.0 (1H, dd, J 7.7, 1.1), 7.80 (1H, d, J 8.1), 7.62-7.43 (3H, m).

Dibenzothiophene-4-tertiarybutoxy carbamate (**3a**) (superior route)



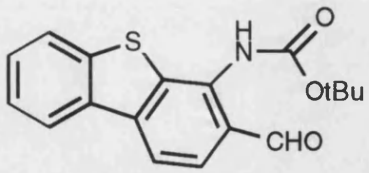
Dibenzothiophene-4-carboxylic acid (**4a**) (1.88g, 8.24mmol) was suspended in t-BuOH (25.0ml) and toluene (25.0ml) and Et_3N (5.7ml, 41.2mmol) was added with stirring at room temperature, to the resultant solution was added DPPA (8.92ml, 41.2mmol) and the mixture stirred at room temperature for 30min before warming to 100°C and stirring for a further 5hrs. The mixture was then allowed to cool and diluted with ethyl acetate, washed with brine solution and the aqueous phase extracted with ethyl acetate (3 x 10ml). The organics were then dried over sodium sulfate, filtered and the solvent evaporated. The orange oil was then purified by flash chromatography on silica eluted with a gradient of 0-5% ethyl acetate/petrol to give carbamate (**3a**) as a white solid (1.889g, 77%). (Found: C, 67.7; H, 5.72; N, 4.67. $C_{17}H_{17}NO_2S$ requires C, 68.22; H, 5.68; N, 4.68%); ν_{max}(Nujol)/cm^{-1} 3335 (NH), 1697 (C=O); δ_H (270MHz; $CDCl_3$) 8.15-8.11 (1H, m), 7.94-7.84 (3H, m), 7.49-7.42 (3H, m), 6.42 (1H, s, NH), 1.57 (9H, s, t-Bu); δ_C (100MHz; $CDCl_3$) 153.6 (C*i*), 139.1 (C*i*), 137.5 (C*i*), 137.0 (C*i*), 133.8 (C*i*), 127.8 (CH), 126.4 (CH), 125.3 (CH), 123.7 (CH), 122.8 (CH), 119.2 (CH), 118.0 (CH), 32.1 (C*i*), 29.2 (3 CH_3); m/z (E.I.) 299 (M^+, 80%).

Dibenzofuran-4-tertiarybutoxy carbamate (**3b**)



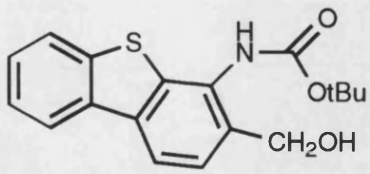
Dibenzofuran-4-carboxylic acid (**4b**) (2.50g 11.8mmol) was suspended in a 1:1 mixture of toluene and t-BuOH (50.0ml) at room temperature to this was added Et_3N (4.9ml 35.4mmol) followed by DPPA (7.6ml, 35.4mmol). The solution was stirred at room temperature for 1hr (complete conversion the acyl azide by t.l.c.) and then heated to reflux at 100°C for 3hr after which time there was no acyl azide remaining by t.l.c.. The mixture was allowed to cool to room temperature before washing with brine (3 x 50ml), drying over sodium sulfate, filtering and removal of solvent under reduced pressure. The oily residue was then dissolved in THF and added dropwise to an ice-cold suspension of excess $SnCl_2$ in water. The mixture was then allowed to warm to room temperature and stirred for 30min until no excess DPPA remained by t.l.c.. The reaction mixture was extracted with ethyl acetate (3 x 100ml), the organics were dried over sodium sulfate, filtered and solvent removed under reduced pressure. The resulting creamy solid was then purified by flash chromatography on silica eluted with 5-30% ethyl acetate/petrol, recrystallisation from ethyl acetate then gave carbamate (**3b**) as a white crystalline solid (3.65g 73%). (Found: C, 71.80; H, 6.03; N, 4.86. $C_{17}H_{17}NO_3$ requires C, 72.08; H, 6.00; N, 4.94%); ν_{max} (Nujol)/cm^{-1} 3267 (NH), 1694 (C=O); δ_H (270MHz; $CDCl_3$) 8.10 (1H, bd, J 7.5), 7.93 (1H, m), 7.57 (2H, td, J 7.9, 1.1), 7.45 (1H, td, J 7.2, 1.3), 7.38-7.22 (2H, m), 7.11 (1H, bs, NH), 1.57 (9H, s, t-Bu); δ_C (100MHz; $CDCl_3$) 155.6 (C*i*), 152.5 (C*i*), 145.7 (C*i*), 127.0 (CH), 124.5 (C*i*), 124.1 (2C*i*), 123.3 (CH), 122.9 (CH), 120.8 (CH), 116.1 (CH), 114.3 (CH), 111.5 (CH), 80.9 (C*i*), 28.2 (CH3); m/z (FAB) 283 (M^+, 21%), 284 (MH^+, 8).

Dibenzothiophene-4-tertiarybutoxy carbamyl-3-carboxaldehyde (**5**)



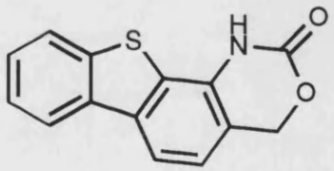
Dibenzothiophene-4-tertiarybutoxy carbamate (**3a**) (100mg, 0.34mmol) was dissolved in ether (2.5ml) at room temperature with stirring. The mixture was cooled to -78°C and t-BuLi (0.80ml, 1.02mmol of a 1.27M solution in hexane) was added dropwise. After stirring at -78°C for 1hr the mixture was allowed to warm to 0°C and stirred for a further 2hrs, resulting in a pale orange solution. The mixture was recooled to -78°C and DMF (0.03ml, 0.37mmol) was added resulting in formation of a pale cream precipitate. The mixture was allowed to warm to room temperature and stirred for 1hr before quenching with a solution of ammonium chloride (10ml). The separated aqueous layer was extracted with ether (3 x 10ml). The combined organics were dried over sodium sulfate, filtered and the solvent evaporated. The crude solid was purified by flash chromatography on silica eluted with 5-10% ethyl acetate/petrol to give the aldehyde (**5**) as a pale yellow solid (81mg, 72%). $\nu_{max}(CHCl_3)/cm^{-1}$ 3011 (NH), 1724 (C=O urethane), 1607 (C=O aldehyde), 1597 (amide); δ_H (270MHz; $CDCl_3$) 10.05 (1H, s, CHO), 9.54 (1H, bs, NH), 8.13 (1H, d, J 7.2), 8.01 (1H, d, J 8.1), 7.85 (1H, d, J 7.3), 7.70 (1H, d, 8.3), 7.55-7.42 (2H, m), 1.59 (9H, s, t-Bu); δ_C (100MHz; $CDCl_3$) 193.3 (CHO), 152.5 (C=O), 142.0 (C*i*), 141.9 (C*i*), 135.7 (C*i*), 133.9 (C*i*), 133.2(C*i*), 129.9 (CH), 128.4 (CH), 124.4 (CH), 123.3 (C*i*), 122.5 (CH), 122.4 (CH), 117.2 (CH), 81.6 (C*i* t-Bu), 28.1 (CH_3 t-Bu); m/z (E.I.) 327 (M^+, 75%).

Dibenzothiophene-4-tertiarybutoxy carbamyl-3-methyl alcohol (**6**)



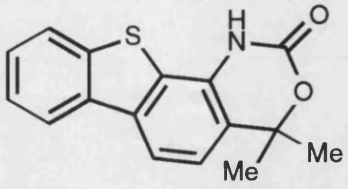
Dibenzothiophene-4-tertiarybutoxycarbamyl-3-carboxaldehyde (**5**) (58mg, 0.18mmol) was dissolved in ethanol (5.0ml) and $NaBH_4$ (8mg, 0.20mmol) was added with stirring at room temperature. After 20min the reaction was quenched with water (10ml) and the separated aqueous phase extracted with DCM (3 x 10ml). The organics were dried over sodium sulfate, filtered and the solvent evaporated to give the alcohol (**6**) as a white solid (51mg, 86%). $\nu_{max}(CHCl_3)/cm^{-1}$ 3389 (OH), 3013 (NH), 1707 (C=O); δ_H (270MHz; $CDCl_3$) 8.13-8.10 (1H, m), 8.03 (1H, d, J 8.1), 7.89-7.82 (1H, m), 7.52 (1H, d, J 7.9), 7.48-7.44 (2H, m), 6.67 (1H, NH), 4.75 (2H, d, J 5.5, CH_2), 3.2 (1H, bs, OH), 1.55 (9H, s, t-Bu); m/z (E.I.) 329 (M^+, 55%). Carried through directly to the next step without purification.

Dibenzothiophene Urethane (**7a**)



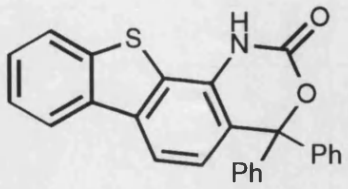
Dibenzothiophene-4-tertiarybutoxycarbamyl-3-methyl alcohol (**6**) (145mg, 0.44mmol) was dissolved in THF (1.0ml) and cooled to 0°C with stirring. NaH (19mg, 0.48mmol of a 60% slurry in mineral oil) was added all at once. After the initial effervescence had subsided the mixture was allowed to warm to room temperature and stirred for 1.5hrs. The reaction was quenched by addition of a solution of ammonium chloride (1ml) and the separated aqueous phase extracted with DCM (3 x 10ml). The organics were dried over sodium sulfate, filtered and the solvent evaporated to give the urethane (**7a**) as a white solid (104mg, 93%). $\nu_{max}(Nujol)/cm^{-1}$ 1707 (C=O); δ_H (270MHz; DMSO-d6) 8.76 (1H, d, J 5.9), 8.48-8.44 (2H, m), 7.96-7.93 (2H, m), 7.78 (1H, d, J 7.7), 5.88 (2H, s, CH_2), 3.80 (1H, s, NH); δ_C (100MHz; DMSO-d6) 152.0 (C*i*), 138.8 (C*i*), 136.7 (C*i*), 135.1 (C*i*), 131.5 (C*i*), 127.6 (CH), 125.1 (CH), 123.9 (C*i*), 123.4 (CH), 122.4 (CH), 121.6 (CH), 117.0 (C*i*), 116.3 (CH), 67.9 (CH_2); m/z (C.I.) 256 (MH^+, 100%), 211 (MH^+ - 44, 10), (Found: M^+ 255.035297. $C_{14}H_9O_2NS$ requires M, 255.035400).

Dibenzothiophene dimethyl urethane (**7b**)



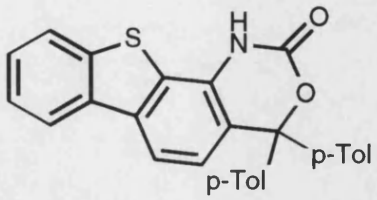
Dibenzothiophene-4-tertiarybutoxy carbamate (**3a**) (100mg, 0.34mmol) was dissolved in ether (2.5ml) at room temperature with stirring. The mixture was cooled to -78°C and t-BuLi (0.80ml, 0.99mmol of a 1.27M solution in hexane) was added dropwise. After stirring at -78°C for 1hr the mixture was allowed to warm to 0°C and stirred for a further 2hrs, resulting in a pale orange solution. The mixture was recooled to -78°C and acetone (0.05ml, 0.66mmol) was added dropwise, the mixture was allowed to warm to room temperature and stirred for 3.5 hrs resulting in a pale cream precipitate. The reaction was quenched by addition of a solution of ammonium chloride (10ml) and the separated aqueous phase extracted with ethyl acetate (3 x 10ml). The organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 5-30% ethyl acetate/petrol gave the dimethyl urethane (**7b**) as a white solid (62mg, 67%). (Found: C, 67.76; H, 4.50; N, 4.82. $C_{16}H_{13}NO_2S$ requires C, 67.84; H, 4.59; N, 4.95%); ν_{max}(Nujol)/cm^{-1} 1720 (C=O); δ_H (270MHz; $CDCl_3$) 8.43 (1H, s, NH), 8.16-8.13 (1H, m), 7.92-7.89 (1H, m), 7.87 (1H, d, J 8.1), 7.51-7.48 (2H, m), 7.27 (1H, d, J 7.1), 1.84 (6H, s, Me);δ_C (100MHz; DMSO-d6) 150.5 (C*i*), 138.6 (C*i*), 136.2 (C*i*), 134.7 (C*i*), 129.5 (C*i*), 127.3 (CH), 124.8 (CH), 124.3 (C*i*), 124.0 (C*i*), 123.0 (CH), 122.0 (CH), 120.5 (CH), 116.3 (CH), 81.6 (C*i*), 27.7 (CH_3); m/z (E.I.) 283 (M^+, 100%).

Dibenzothiophene diphenyl urethane (**7c**)



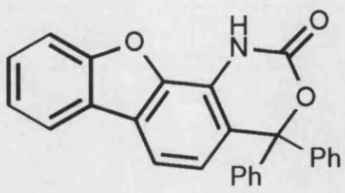
Dibenzothiophene-4-tertiarybutoxy carbamate (**3a**) (100mg, 0.34mmol) was dissolved in ether (1.0ml) at room temperature with stirring. The mixture was cooled to -78°C and t-BuLi (0.61ml, 0.84mmol of a 1.38M solution in hexane) was added dropwise. After stirring at -78°C for 1hr the mixture was allowed to warm to 0°C and stirred for a further 2hrs, resulting in a pale orange solution. The mixture was recooled to -78°C and benzophenone (122mg, 0.67mmol) in ether (1.0ml) was added dropwise, the mixture was allowed to warm to room temperature and stirred over night resulting in a pale cream precipitate. The reaction was quenched by addition of a solution of ammonium chloride (10ml) and the separated aqueous phase extracted with ethyl acetate (3 x 10ml). The organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 10-30% ethyl acetate/petrol gave the diphenyl urethane (**7c**) as a white solid (132mg, 97%). (Found: C, 76.5; H, 4.02; N, 3.42. $C_{26}H_{17}NO_2S$ requires C, 76.6; H, 4.17; N, 3.44%); ν_{max}(Nujol)/cm^{-1} 1713 (C=O); δ_H (270MHz; $CDCl_3$) 8.45 (1H, s, NH), 8.15-8.12 (1H, m), 7.92-7.88 (1H, m), 7.81 (1H, d, J 8.1), 7.54-7.46 (2H, m), 7.36-7.29 (6H, m), 7.28-7.24 (4H, m), 6.82 (1H, d, J 8.1); δ_C (100MHz; $CDCl_3$) 151.7 (C*i*), 141.3 (C*i*), 139.0 (C*i*), 137.5 (C*i*), 135.2 (C*i*), 128.7 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 125.0 (CH), 124.4 (CH), 123.2 (CH), 122.9 (C*i*), 122.0 (CH), 115.0 (CH); m/z (C.I.) 408 (MH^+, 25%).

Dibenzothiophene di-p-tolyl urethane (**7d**)



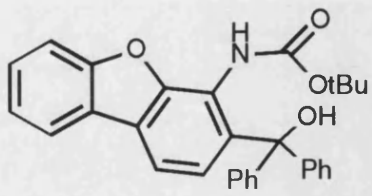
Dibenzothiophene-4-tertiarybutoxy carbamate (**3a**) (200mg, 0.67mmol) was dissolved in ether (3.0ml) at room temperature with stirring. The mixture was cooled to -78°C and t-BuLi (1.2ml, 0.84mmol of a 1.38M solution in hexane,) was added dropwise. After stirring at -78°C for 1hr the mixture was allowed to warm to 0°C and stirred for a further 2hrs, resulting in a pale orange solution. The mixture was recooled to -78°C and 4,4'-dimethyl benzophenone (280mg, 1.34mmol) in ether (2.0ml) was added dropwise, the mixture was allowed to warm to room temperature and stirred over night resulting in a pale cream precipitate. The reaction was quenched by addition of a solution of ammonium chloride (10ml) and the separated aqueous phase extracted with ethyl acetate (3 x 10ml). The organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 10-100% ethyl acetate/petrol gave the di-*p*-tolyl urethane (**7d**) as a white solid (218mg, 75%). ν_{max}(Nujol)/cm^{-1} 1719 (C=O); δ_H (270MHz; $CDCl_3$) 8.15-8.12 (1H, m), 7.91-7.88 (1H, m), 7.83 (1H, s, NH), 7.79 (1H, d, J 8.3), 7.54-7.46 (2H, m), 7.136 (8H, m), 6.83 (1H, d, J 8.2), 2.35 (6H, s, Me); δ_C (100MHz; $CDCl_3$) 150.7 (C*i*), 138.8 (C*i*), 138.6 (C*i*), 137.9 (C*i*), 136.9 (C*i*), 134.6 (C*i*), 130.9 (C*i*), 128.7 (CH), 127.4 (CH), 124.9 (CH), 124.6 (C*i*), 123.9 (CH), 123.3 (C*i*), 123.1 (CH), 122.1 (CH), 115.6 (CH), 88.2 (CH), 20.57 (CH_3); m/z (FAB) 436 (MH^+, 100%), 458 (MNa^+, 21), (Found: MH^+ 436.1370. $C_{28}H_{21}NO_2S$ requires MH, 436.1371).

Dibenzofuran diphenyl urethane (**7e**)



Dibenzofuran-4-tertiarybutoxy carbamate (**3b**) (1.0g, 3.53mmol) was dissolved in ether (5.0ml) and cooled to -78°C with stirring. To this was added t-BuLi (4.54ml, 7.4mmol of a 1.63M solution in hexane) and the egg yellow suspension stirred at this temperature for 30min. The mixture was then allowed to warm to 0°C and stirred for a further 2hrs to give a pale yellow suspension. The mixture was then recooled to -78°C and benzophenone (1.28g 7.06mmol) in ether (5.0ml) was added dropwise. After complete addition the mixture was allowed to warm to room temperature and stirred for 4 days. After this time cyclisation was observed to be incomplete but the reaction was quenched by the addition of a solution of ammonium chloride (20ml) and the products extracted into DCM (3 x 50ml), dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The products were separated by flash chromatography on silica eluted with 30% ethyl acetate/petrol followed by 5% ethyl acetate/DCM to give (**7e**) as a white solid (1.7g, 62%) and (0.664g, 20%) of the uncyclised material (**7f**) as a white solid. This uncyclised product (**7f**) was redissolved in ether (10.0ml) and NaH (0.122g 3.06mmol of a 60% suspension in mineral oil) was added with stirring. After 2hrs at room temperature full cyclisation was achieved and the reaction was worked up as described above. The crude product was recrystallised from ethyl acetate to give (**7e**) (0.474g, 17% with respect to the starting carbamate, 79% overall yield). mp. 180-182°C (from ethyl acetate); ν_{max} (Nujol)/cm^{-1} 3743 (NH), 1710 (C=O); δ_H (270MHz; CDCl3) 7.94 (1H, d, J 7.7), 7.78 (1H, bs, NH), 7.61-7.47 (3H, m), 7.41-7.32 (7H, m), 7.26-7.22 (4H, m), 6.70 (1H, d, J 8.1); δ_C (100MHz ;DMSO-d6) 156.0 (C*i*), 150.3 (C*i*), 142.2 (C*i*), 141.6 (C*i*), 128.6 (CH), 128.4 (CH), 128.2 (CH), 127.6 (CH), 125.1 (C*i*), 124.2 (C*i*), 123.6 (CH), 123.4 (C*i*), 121.9 (CH), 121.6 (CH), 121.5 (C*i*), 114.1 (CH), 111.8 (CH), 88.6 (C*i*); m/z (FAB) 392 (MH^+, 100%), (Found: MH^+ 392.128932. $C_{26}H_{17}NO_3$ requires MH^+ 392.128669).

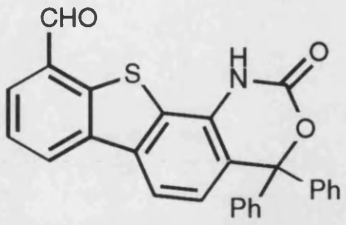
Dibenzofuran-3-(diphenyl)hydroxymethyl-4-tertiarybutoxy carbamate (**7f**)



Dibenzofuran-4-tertiarybutoxy carbamate (**3b**) (6.14g, 21.7mmol) was suspended in ether (40.0ml) and cooled to -78°C. t-BuLi (27ml, 45.6mmol of a 1.7M solution in hexane) was added slowly, dropwise. The custard yellow suspension was stirred at -78°C for 30min and then allowed to warm to 0°C and stirred for a further 2.5hrs. The pale cream suspension was recooled to -78°C and benzophenone (4.7g, 26mmol) was added as a solution in ether (20.0ml). After stirring for 15min at -78°C the mixture was allowed to warm to room temperature and stirred for 16hrs. The reaction was quenched by the addition of a solution of ammonium chloride (20ml) and the aqueous extracted with DCM (3 x 100ml). The combined organics were dried over sodium sulfate, filtered and the solvent evaporated to give a pale yellow foam. Purification by flash chromatography on silica eluted with 0-10% ethyl acetate/DCM gave alcohol (**7f**) as a white solid (6.69g, 67%). (Found: C, 77.03; H, 5.95; N, 2.88. $C_{30}H_{27}NO_4$ requires C, 77.42; H, 5.81; N, 3.01%); ν_{max} (Nujol)/cm^{-1} 3323 (OH), 1705 (C=O); δ_H (400MHz; $CDCl_3$) 7.89 (1H, d, J 7.6), 7.58 (1H, d, J 8.2), 7.55 (1H, d, J 8.2), 7.43 (1H, t, J 7.9), 7.36-7.25 (11H, m), 7.20 (1H, bs, NH), 6.66 (1H, d, J 8.2), 3.79 (1H, bs, OH), 1.25 (9H, s); δ_C (100MHz; $CDCl_3$) 156.8 (C*i*), 152.8 (C*i*), 152.1 (C*i*), 145.8 (C*i*), 138.9 (C*i*), 128.2 (CH), 127.6 (CH), 127.5 (CH), 125.7 (C*i*), 124.3 (CH), 124.0 (C*i*), 122.9 (C*i*), 122.7 (CH), 120.7 (CH), 116.2 (CH), 112.0 (CH), 83.0 (C*i*), 80.0 (C*i*), 28.1 (CH_3); m/z (Thermospray +ve) 392 ($MH\text{-}t\text{-}BuOH^+$, 100%).

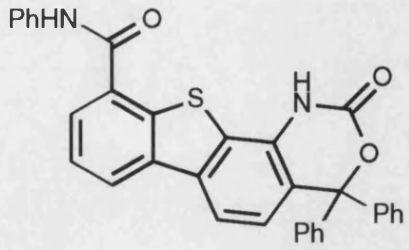
DERIVATISATION OF CYCLIC URETHANES

Dibenzothiophene diphenyl urethane-6-carboxaldehyde **(8a)**



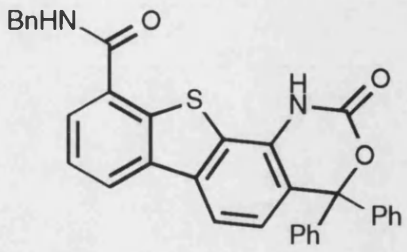
Dibenzothiophene diphenyl urethane (**7c**) (300mg, 0.74mmol) was suspended in ether (3.0ml) and TMEDA (0.33ml, 2.22mmol) was added with stirring at room temperature. The mixture was cooled to -78°C and s-BuLi (1.70ml, 2.22mmol of a 1.3M solution in cyclohexane) was added dropwise. The reaction was warmed to room temperature and stirred for 3hrs to give a dark red solution. The reaction was recooled to -78°C and DMF (0.11ml, 1.48mmol) in ether (3.0ml) was added dropwise and the mixture allowed to warm to room temperature after 1hr the reaction was quenched by addition of a solution of ammonium chloride (10ml) and the separated aqueous phase extracted with DCM (3 x 10ml). The organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 0-5% MeOH/DCM gave the aldehyde (**8a**) as a pale yellow solid (173mg, 54%). $\nu_{max}(CHCl_3)/cm^{-1}$ 3180 (NH), 1733 (C=O urethane), 1656 (C=O aldehyde); δ_H (270MHz; DMSO-d6) 10.97 (1H, s, NH), 10.31 (1H, s, CHO), 8.72 (1H, d, J 8.1), 8.32 (1H, d, J 7.3), 8.17 (1H, d, J 8.1), 7.84 (1H, t, J 8.1), 7.43-7.41 (6H, m), 7.17-7.14 (4H, m), 6.79 (1H, d, J 8.1), [^{1}H-^{1}H COSY and NOESY data allow full assignment, see Appendix Chapter 2]; δ_C (100MHz; DMSO-d6) 192.0 (C*i*), 150.0 (C*i*), 141.0 (C*i*), 136.3 (C*i*), 136.2 (C*i*), 135.3 (C*i*), 131.1 (C*i*), 130.2 (C*i*), 128.5 (CH), 128.3 (2xCH), 127.7 (CH), 127.5 (2 x CH) 127.0 (C*i*), 125.4 (CH), 124.3 (CH), 123.6 (C*i*); m/z (FAB) 436 (MH^+, 30%), (Found: MH^+ 436.0990. $C_{27}H_{18}NO_3S$ requires MH, 436.1007).

Dibenzothiophene diphenyl urethane-6-phenyl amide (**8b**)



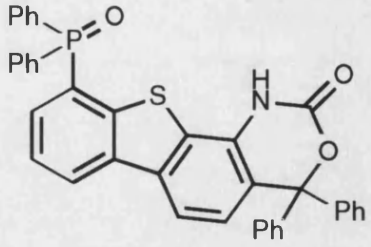
Dibenzothiophene diphenyl urethane (**7c**) (200mg, 0.49mmol) was suspended in ether (2.0ml) and TMEDA (0.22ml, 1.47mmol) was added with stirring at room temperature. The mixture was cooled to -78°C and s-BuLi (1.30ml, 1.47mmol of a 1.3M solution in cyclohexane) was added dropwise. The reaction was warmed to room temperature and stirred for 4hrs to give a dark red solution. The reaction was recooled to -78°C and phenyl isocyanate (0.21ml, 1.96mmol) in ether (2ml) was added dropwise and the mixture allowed to warm to room temperature after 1hr the reaction was quenched by addition of a solution of ammonium chloride (10ml) and the separated aqueous phase extracted with ethyl acetate (3 x 10ml). The organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 10-50% ethyl acetate/petrol and then 0-5% ether/DCM gave the amide (**8b**) as a white solid (129mg, 50%). $\nu_{max}(CHCl_3)/cm^{-1}$ 3401 and 3354 (NH), 1713 and 1660 (C=O); δ_H (270MHz; $CDCl_3$) 8.35 (1H, d, J 8.1), 8.12 (1H, s, NH), 7.94 (1H, d, J 7.5), 7.84 (1H, d, J 8.2), 7.74-7.71 (2H, m), 7.64 (1H, t, J 7.7), 7.46 (1H, t, J 7.7), 7.37-7.35 (6H, m), 7.24-7.20 (7H, m), 6.86 (1H, d, J 8.1); δ_C (67MHz; DMSO-d6) 165 (C=O amide), 151 (C=O urethane), 149 (CH), 141.6 (C*i*), 139 (C*i*), 135 (C*i*), 134.8 (CH), 131 (C*i*), 129 (6 CH), 128.4 (CH), 127.7 (CH), 127 (C*i*), 126 (C*i*), 125 (C*i*), 124 (C*i*), 123 (C*i*), 120.7 (CH), 117 (C*i*); m/z (FAB) 527 (MH^+, 100%), (Found: MH^+ 527.1449. $C_{33}H_{22}N_2O_3S$ requires MH, 527.1429).

Dibenzothiophene diphenyl urethane-6-benzyl amide **(8c)**



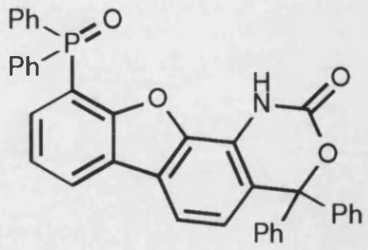
Dibenzothiophene diphenyl urethane (**7c**) (200mg, 0.49mmol) was suspended in ether (2.0ml) and TMEDA (0.22ml, 1.47mmol) was added with stirring at room temperature. The mixture was cooled to -78°C and s-BuLi (1.30ml, 1.47mmol of a 1.3M solution in cyclohexane) was added dropwise. The reaction was warmed to room temperature and stirred for 4hrs to give a dark red solution. The reaction was recooled to -78°C and benzyl isocyanate (0.24ml, 1.96mmol) in ether (2.0ml) was added dropwise and the mixture allowed to warm to room temperature after 1hr the reaction was quenched by addition of a solution of ammonium chloride (10ml) and the separated aqueous phase extracted with DCM (3 x 10ml). The organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 0-5% ether/DCM gave amide (**8c**) as a white solid (137mg, 52%). ν_{max}(Nujol)/cm^{-1} 3248 and 3166 (NH), 1727 (C=O); δ_H (270MHz; DMSO-d6) 9.46 (1H, bs, NH),8.54 (1H, d, J 7.7), 8.23 (1H, d, J 7.7), 8.07 (1H, d, J 8.2), 7.67 (1H, t, J 7.7), 7.42-7.14 (15H, m), 6.72 (1H, d, J 8.1), 4.58 (2H, d, J 5.5, CH_2), [NH seen as inverse peak off scale.]; δ_C (67MHz; DMSO-d6) 165.6 (C=O amide), 150.7 (C=O urethane), 141.6, 139.5, 139.1, 136.3, 130.9, 128.7, 128.4, 127.6, 127.4, 126.9, 125.9, 125.3, 125.0, 123.8, 123.5, 115.9, 88.3, 42.9 (CH_2); m/z (FAB) 541 (MH^+, 52%), (Found: MH^+ 541.1587. $C_{34}H_{24}N_2O_3S$ requires MH^+, 541.1585).

Dibenzothiophene diphenyl urethane-6-(diphenyl)phosphine oxide **(8d)**



Dibenzothiophene diphenyl urethane (**7c**) (100mg 0.24mmol) was suspended in ether (0.5ml) and TMEDA (0.11ml, 0.72mmol) was added with stirring. The mixture was cooled to -78°C and s-BuLi (0.56ml, 0.72mmol of a 1.3M solution in cyclohexane) was added dropwise with stirring. After complete addition the mixture was allowed to warm to room temperature and stirred for a further 3hrs to give a dark red suspension. This was then recooled to -78°C and diphenyl phosphoryl chloride (0.11ml, 0.6mmol) in ether (1.0ml) was added dropwise. After warming to room temperature the mixture was stirred for 1hr before quenching with a solution of ammonium chloride (5ml), extracting into DCM (3 x 10ml), drying over sodium sulfate, filtering and solvent removal under reduced pressure. The product was purified by flash chromatography on silica eluted with 60% ethyl acetate/petrol and then recrystallised from DCM/Hexane to give (**8d**) as a white solid (81mg, 56%). ν_{max}(Nujol Mull)/cm^{-1} 1734 (C=O), 1172 (P=O); δ_H (270MHz; $CDCl_3$) 8.32-8.28 (1H, m), 7.85-7.62 (5H, m), 7.59-7.41 (9H, m), 7.34-7.18 (10H, m), 6.83 (1H, d, J 8.2); δ_C (100MHz; $CDCl_3$) 150.8 (C*i*), 142.3 (C*i*, d, J_{C-P} 6), 141.28 (C*i*), 136.6 (C*i*, d, J_{C-P} 9), 135.9 (C*i*), 132.4 (CH), 132.2 (CH, d, J_{C-P} 11), 132.0 (CH, d, J_{C-P} 11), 131.4 (C*i*), 130.3 (C*i*, d, J_{C-P} 4), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.6 (C*i*), 126.4 (C*i*, d, J_{C-P} 33), 125.4 (CH), 124.5 (CH, d, J_{C-P} 13), 124.4 (CH), 123.4 (C*i*), 115.6 (CH), 89.9 (C*i*); δ_P (160MHz, $CDCl_3$) 29.84 (s); m/z (FAB) 608 (MH^+, 100%), (Found: 608.147771. $C_{38}H_{26}NO_3PS$ requires MH, 608.144929).

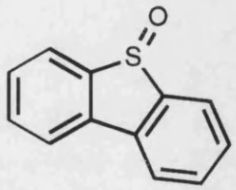
Dibenzofuran diphenyl urethane-6-(diphenyl)phosphine oxide (**8e**)



Dibenzofuran diphenyl urethane (**7e**) (200mg, 0.512mmol) was suspended in ether (1.0ml) and TMEDA (0.23ml, 1.53mmol) added with stirring at room temperature. The suspension was cooled to -78°C and s-BuLi (1.18ml, 1.53mmol of a 1.3M solution in cyclohexane) was added dropwise. The mixture was then allowed to warm to room temperature resulting in a dark, wine red suspension. After 3hrs at room temperature the suspension was recooled to -78°C and diphenyl phosphoryl chloride (0.29ml, 1.53mmol) in ether (2.0ml) was added dropwise. After complete addition the mixture was allowed to warm to room temperature and stirred for 1hr before quenching with a solution of ammonium chloride (1ml). The aqueous phase was extracted with DCM (3 x 10ml), the organics were then dried over sodium sulfate, filtered and the solvent evaporated to give a yellow oil. Purification by flash column chromatography on silica eluted with 40% ethyl acetate/petrol gave (**8e**) as a white solid (147mg, 49%).ν_{max}($CHCl_3$ film)/cm^{-1} 1732 (C=O), 1214 (P=O); δ_H (270MHz; $CDCl_3$) 9.76 (1H, s, NH), 8.15-8.13 (1H, m), 7.73-7.44 (11H, m), 7.43-7.17 (12H, m), 6.72 (1H, d, J 8.1); δ_C (100MHz; $CDCl_3$) 157.6 (C*i*), 151.0 (C*i*), 142.8 (C*i*), 141.4 (C*i*), 132.5 (CH), 131.9 (CH), 131.7 (CH, d, J_{C-P} 11), 130.6 (C*i*), 128.7 (CH, d, J_{C-P} 13), 128.5 (CH), 128.1 (CH, d, J_{C-P} 6), 125.4 (CH), 125.0 (C*i*, d, J_{C-P} 7), 124.3 (C*i*, d, J_{C-P} 48), 123.2 (CH, d, J_{C-P} 11), 122.6 (CH), 122.0 (C*i*), 116.9 (C*i*), 115.8 (C*i*), 113.5 (CH), 89.7 (C*i*); δ_P (160MHz, $CDCl_3$) 28.14 (s); m/z (Electrospray) 592 (MH^+, 100%), (Found: 592.16784. $C_{38}H_{26}NO_4P$ requires MH, 592.16772).

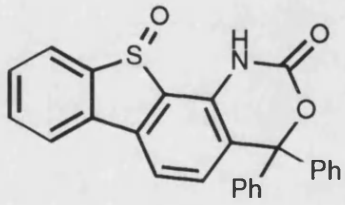
(S)-DERIVATISATION OF DIBENZOTHIOPHENE RECEPTORS

Dibenzothiophene-S-oxide (**9**)[38]



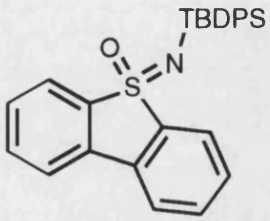
Dibenzothiophene (1.0g, 5.35mmol) was dissolved in DCM (30ml) with stirring at room temperature and *m*-CPBA (1.9g, 5.35mmol) was added. After 1hr the reaction was quenched by the addition of sodium bicarbonate solution (10ml) and the aqueous phase extracted with DCM (3 x 50ml). The organics were dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica eluted with a gradient of 1-10% MeOH/DCM to give sulfoxide (**9**) (520mg, 52%) as a white solid, the remainder being starting material mixed with the sulfone compound. $\nu_{max}(CHCl_3$ film)/cm^{-1} 1067 and 1025 (S=O); δ_H (270MHz; $CDCl_3$) 8.00 (2H, dd, J 7.5), 7.83 (2H, dd, J 7.3), 7.61 (2H, td, J 7.5, 1.1), 7.51 (2H, td, J 7.5, 1.3); m/z (E.I.) 200 (M^+, 100%).

Dibenzothiophene diphenyl urethane-S-oxide (**11**)



Dibenzothiophene diphenyl urethane (**7c**) (50mg, 0.123mmol) was dissolved in DCM (4.0ml) with stirring at room temperature and *m*-CPBA (42mg, 0.123mmol of a 50% solid) was added. After 40min the reaction was quenched by the addition of sodium bicarbonate solution (5ml) and the aqueous phase extracted with DCM (3 x 10ml). The organics were dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica eluted with a gradient of 0-10% ether/DCM to give sulfoxide (**11**) (32mg, 62%) as a white solid, the remainder being starting material mixed with the sulfone compound. $\nu_{max}(CHCl_3)/cm^{-1}$ 3142 (NH), 1733 (C=O), 1013 (S=O); δ_H (270MHz; $CDCl_3$) 8.46 (1H, s, NH), 8.10 (1H, d, J 7.3), 7.81 (1H, d, J 7.7), 7.63 (1H, d, J 8.8), 7.59-7.54 (2H, m), 7.43 (1H, d, J 7.9), 7.39-7.34 (6H, m), 7.25-7.21 (4H, m), 6.94 (1H, d, J 7.9); m/z (FAB) 424 (MH^+, 100%), 446 (MNa^+, 85), (Found: MH^+ 424.1021. $C_{26}H_{17}O_3NS$ requires MH, 424.1007).

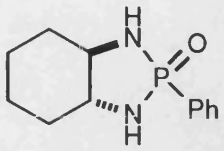
Dibenzothiophene N-TBDPS sulfoximine (**13**)



Dibenzothiophene-S-oxide (**9**) (100mg, 0.5mmol) was dissolved in DCM (3.0ml) and mesitylene sulfonyl hydroxylamine (179mg, 0.83mmol) was added with stirring at room temperature. After 6 days a pink suspension resulted. The solvent was removed under reduced pressure and then taken up in dry DMF (3.0ml) and imidazole (170mg, 2.5mmol) was added with stirring at room temperature for 30min. TBDPSCl (0.26ml, 1.0mmol) was added and the mixture allowed to stir at room temperature for 16hrs. The reaction was quenched by the addition of a solution of ammonium chloride (5ml) and the separated aqueous phase extracted with DCM (3 x 10ml). The organics were dried over sodium sulfate, filtered and the solvent removed under reduced pressure to give a cream solid. Subsequent purification by flash chromatography on silica eluted with a gradient of 0-40% ethyl acetate/petrol gave (**13**) as an orange solid (82mg, 35%). ν_{max}(Nujol)/cm^{-1} 1302, 1173, 1108, 820; δ_H (270MHz; $CDCl_3$) 7.61-7.53 (6H, m), 7.45-7.20 (12H, m), 1.03 (9H, s, t-Bu); δ_C (100MHz; $CDCl_3$) 142.0 (C*i*), 135.3 (CH), 135.1 (C*i*), 132.0 (CH), 130.6 (C*i*), 129.7 (CH), 128.9 (CH), 127.3 (CH), 121.1 (CH), 120.9 (CH), 76.2 (CH_3); m/z (C.I.) 454 (MH^+, 30%).

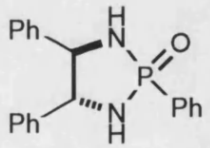
SYNTHESIS OF DIAZAPHOSPHOLIDINE OXIDE RECEPTORS

(R_{3a},R_{7a})-2-phenyl-2,3,3a,4,5,6,7,7a-octahydro-1H-1,3,2-benzodiazaphosphole 2-oxide **(19)**[117]



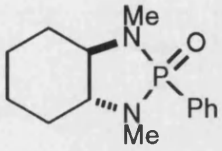
(R,R)-(-)-1,2-diamino cyclohexane (**15**) (1.0g, 8.76mmol) was dissolved in DCM (50.0ml) and triethylamine (4.87ml, 35.04mmol) was added and the mixture cooled to 0°C. Phenyl phosphinic dichloride (1.7g, 8.76mmol) was added slowly dropwise. After 30min the mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of water and the separated organics were dried over sodium sulfate, filtered and the solvent evaporated to give (**19**) as a pale yellow solid (1.34g, 65%). $[\alpha]^{20}_D$ = + 4.0 (*c* = 0.49, methanol) [cf. lit.[117] $[\alpha]^{20}_D$ = + 4.3 (*c* = 0.51, methanol)]; δ_H (400MHz, $CDCl_3$) 7.92- 7.87 (2H, m), 7.51-7.40 (3H, m), 3.30 (1H, m), 3.08-3.02 (1H, m), 2.96 (1H, d, J 12.2), 2.86 (1H, d, J 5.9), 1.95 (1H, m), 1.85 (1H, m), 1.81 (2H, s), 1.56-1.35 (4H, m).

(S_3,S_4)-1-Phenyl-(3,4-diphenyl)-diazaphospholidine 1-oxide **(18)**[118]



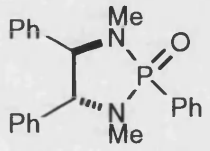
Prepared as for (**19**) in quantitative yield. δ_H (270MHz, $CDCl_3$) 8.11-8.04 (2H, m), 7.54 (3H, s), 7.29 (7H, s), 7.20 (3H, s), 4.69 (1H, d, J 8.8), 4.53 (1H, d, J 8.8), 3.30 (1H, d, 15.4), 3.24 (1H, d, J 9.0).

(R_{3a},R_{7a})-1,3-(dimethyl)-2-phenyl-2,3,3a,4,5,6,7,7a-octahydro-1H-1,3,2-benzodiazaphosphole 2-oxide (**21**)



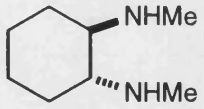
(**19**) (1.0g, 4.24mmol) was dissolved in THF (20.0ml) and cooled to 0°C. n-BuLi (3.4ml, 8.53mmol of 2.5 solution in hexanes) was added dropwise. The resulting orange solution was stirred for 1hr before dropwise addition of methyl iodide (0.53ml, 8.52mmol). After 1.5hrs at room temperature the reaction was quenched by the addition of water and the aqueous extracted with DCM (3 x 20ml). The combined organics were dried over sodium sulfate, filtered and solvent evaporated to give (**21**) as a white solid (1.15g, 100%). $[\alpha]^{20}_D$ = - 29.5 (c = 0.9, $CHCl_3$); ν_{max}($CHCl_3$ film)/cm^{-1} 1441 (P-Ar), 1250 (P=O); δ_H (270MHz, $CDCl_3$) 7.80-7.72 (2H, m), 7.54-7.41 (3H, m), 2.97-2.89 (1H, m), 2.66-2.53 (4H, m), 2.28 (3H, d, J 11.2), 2.12 (1H, m), 2.01-1.98 (1H, m), 1.88-1.85 (4H, m), 1.39-1.21 (4H, m); δ_C (100MHz, $CDCl_3$) 132.7 (CH), 131.5 (CH), 130.0 (C*i*), 128.3 (CH), 65.5 (CH), 63.7 (CH), 28.8 (CH_3), 28.3 (CH_2), 24.4 (CH_2); δ_P (160MHz, $CDCl_3$) 34.1 (s); m/z (CI) 265 (MH^+, 100%), (Found: 265.146084. $C_{14}H_{21}N_2OP$ requires MH, 265.146977).

(S_3,S_4)-1-Phenyl-N,N'-dimethyl-(3,4-diphenyl)-diazaphospholidine 1-oxide (**20**)[118]



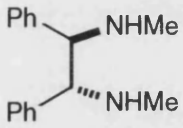
Prepared as for (**21**) in 96% yield. δ_H (270MHz, $CDCl_3$) 8.03-7.95 (2H, m), 7.64-7.53 (3H, m), 7.33-7.10 (10H, m), 4.25 (1H, d, J 8.8), 4.10 (1H, d, J 8.6), 2.44 (3H, d, J 10.6), 2.20 (3H, d, J 9.9).

(R,R)-N,N'-dimethyl-1,2-diamino cyclohexane (**17**)[1]



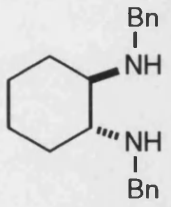
(**21**) (2.56g, 9.70mmol) was dissolved in methanol (20.0ml) and to this was added 0.8M HCl/Methanol (20.0ml) and the mixture stirred at reflux for 24hrs. The pale yellow solution was cooled to room temperature and the solvent evaporated to give a brown solid. Crystallisation from IPA gave the diamine hydrochloride salt as a white crystalline solid. The salt was dissolved in saturated potassium carbonate solution and extracted into DCM (3 x 30ml). The organics were dried over potassium carbonate, filtered and solvent evaporated to give diamine (**17**) as a white, waxy solid (910mg, 66%). $[\alpha]^{20}_D$ = - 140.2 (*c* = 4.05, $CHCl_3$) [cf. lit.[1] $[\alpha]^{20}_D$ = - 145.7 (*c* = 4.47, $CHCl_3$)]; δ_H (400MHz, $CDCl_3$) 2.39 (6H, s), 2.12-2.01 (4H, m), 1.74-1.65 (4H, m), 1.28-1.16 (2H, m), 0.99-0.94 (2H, m).

(S,S)-N,N'-dimethyl-1,2-diphenyl ethylenediamine (**16**)[1]



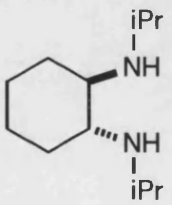
Prepared as described for (R,R)-N,N'-dimethyl-1,2-diamino cyclohexane (**17**) in 84% yield. $[\alpha]^{20}_D$ = - 18.0 (*c* = 0.155, $CHCl_3$) [cf. lit.[1] $[\alpha]^{20}_D$ = - 18.0 (*c* = 1.0, $CHCl_3$)]; δ_H (270MHz, $CDCl_3$) 7.16-7.09 (6H, m), 7.05-7.02 (4H, m), 3.57 (2H, s), 2.47 (2H, bs), 2.26 (6H, s).

(R,R)-N,N'-dibenzyl-1,2-diamino cyclohexane[77]



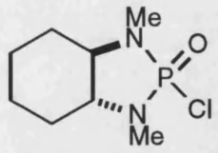
(R,R)-1,2-diamino cyclohexane (**15**) (1.0g, 8.77mmol) was dissolved in anhydrous MeOH (5.0ml) and heated to reflux. Benzaldehyde (1.78ml, 17.54mmol) was added dropwise over a period of 2mins and the mixture stirred at reflux for 30mins. The solution was allowed to cool to room temperature and sodium borohydride (700mg, 18.42mmol) was added portionwise. After the vigorous effervescence had subsided the mixture was heated to reflux for 15mins. The reaction was then quenched by the addition of water (5ml) and the aqueous phase extracted with DCM (3 x 10ml). The separated organics were dried over potassium carbonate, filtered and the solvent evaporated to give the diamine as a waxy solid (2.60g, 100%). $[\alpha]^{20}_D$ = - 80.0 (*c* = 2.5, $CHCl_3$), (not previously reported); δ_H (250MHz, $CDCl_3$) 7.40-7.15 (10H, m), 3.90 (2H, d, J 13.1), 3.65 (2H, d, J 13.1), 2.30-2.10 (4H, m), 1.87 (2H, bs, NH), 1.81-1.60 (2H, m), 1.30-0.90 (4H, m).

(R,R)-N,N'-diisopropyl-1,2-diamino cyclohexane[1]



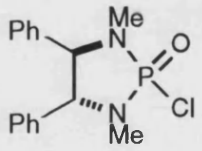
(R,R)-1,2-diamino cyclohexane (**15**) (1.0g, 8.77mmol) was dissolved in EtOH (30.0ml) and acetone (3.21ml, 43.85mmol) was added. The mixture was then subjected to atmospheric hydrogenation in the presence of platinum oxide (Adam's Catalyst) (50mg). After stirring for 24hrs the catalyst was removed by filtration through a plug of celite and the solvent removed under reduced pressure to give the diamine as a colourless oil (1.62g, 93%). $[\alpha]^{20}_D$ = - 120.0 (*c* = 2.5, $CHCl_3$) [cf. lit.[1] $[\alpha]^{20}_D$ = - 125.2 (*c* = 9.64, $CHCl_3$)]; δ_H (250MHz, $CDCl_3$) 2.94-2.79 (2H, m), 2.20-2.00 (4H, m), 1.75-1.60 (2H, m), 1.28-1.15 (2H, m), 1.10-0.85 (16H, m); m/z (thermospray) 199 (MH+, 90%).

(R_{3a},R_{7a})-1,3-(dimethyl)-2-chloro-2,3,3a,4,5,6,7,7a-octahydro-1H-1,3,2-benzodiazaphosphole 2-oxide (**23**)[1]



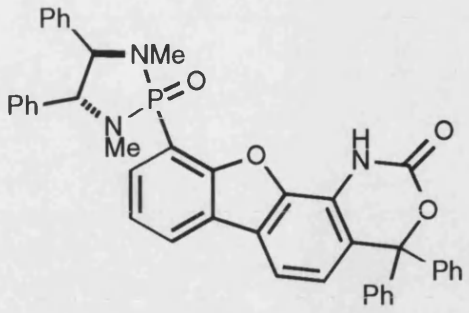
(R,R)-N,N'-dimethyl-1,2-diamino cyclohexane (**17**) (450mg, 3.19mmol) was dissolved in DCM (60.0ml) and triethylamine (1.33ml, 9.57mmol) was added with stirring. The mixture was cooled to 0°C and $P(O)Cl_3$ (0.3ml, 3.19mmol) was added slowly dropwise. The mixture was gradually allowed to warm to room temperature over night. The reaction was quenched by the addition of water (60ml) and the separated organics dried over sodium sulfate, filtered and solvent evaporated. Purification by suction flash chromatography on silica eluted with 50% ethyl acetate/cyclohexane gave (**23**) as a white solid (673mg, 95%). $[\alpha]^{20}_D$ = - 54.09 (*c* = 1.0, CH_2Cl_2) [cf. lit.[1] $[\alpha]^{20}_D$ = - 57.7 (*c* = 5.7, CH_2Cl_2)]. δ_H (250MHz, $CDCl_3$) 2.90-2.81 (1H, m), 2.67 (3H, d, J 11.9), 2.64-2.53 (1H, m), 2.55 (3H, d, J 15.9), 2.04-2.00 (2H, m), 1.87 (2H, m), 1.36-1.18 (4H, m).

(S_3,S_4)-1-Chloro-N,N'-dimethyl-(3,4-diphenyl)-diazaphospholidine 1-oxide (**22**)[1]



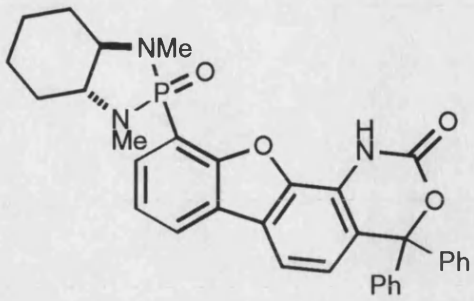
Prepared as described for (**23**) in 87% yield. δ_H (270MHz, $CDCl_3$) 7.36-7.31 (6H, m), 7.15-7.12 (2H, m), 7.08-7.05 (2H, m), 4.17-4.10 (1H, m), 3.84 (1H, d, J 8.6), 2.60 (3H, d, J 10.4), 2.45 (3H, d, J 14.5).

(S_3,S_4)-2-(dibenzofuran diphenyl urethan-6-yl)-N,N'-dimethyl-(3,4-diphenyl)-diazaphospholidine 1-oxide **(24)**



Dibenzofuran diphenyl urethane (**7e**) (170mg, 0.4mmol) was suspended in ether (0.5ml) and TMEDA (0.2ml, 1.31mmol) was added. The mixture was cooled to -78°C and s-BuLi (1.0ml, 1.31mmol of a 1.3M solution in cyclohexane) was added dropwise. After 15min the mixture was allowed to warm to room temperature and stirred for 3hrs. The resulting dark red suspension was recooled to -78°C and the chloro diazaphospholidine oxide (**22**) (278mg, 0.87mmol) in THF (2.0ml) was added slowly. The resulting orange suspension was allowed to warm to room temperature and then stirred overnight. The reaction was quenched by the addition of water and the aqueous phase extracted with ether (3 x 10ml). The combined organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 60-70% ethyl acetate/petrol followed by recrystallisation from ethyl acetate/petrol gave (**24**) (96mg, 33%). $[\alpha]^{20}_D$ = -96.5 (*c* = 1.0, $CHCl_3$); ν_{max}(Nujol Mull)/cm^{-1} 3743, 3485 (NH), 1738 (C=O), 1245 (P=O); δ_H (270MHz, $CDCl_3$) 9.65 (1H, s, NH), 8.18 (1H, d, J 7.7), 8.06-7.98 (1H, m), 7.60-7.54 (2H, m), 7.38-7.21 (18H, m), 7.13-7.11 (2H, m), 6.76 (1H, d, J 8.1), 4.37-4.25 (2H, AB overlapping, J 8.4), 2.55 (3H, d, J 10.4), 2.32 (3H, d, J 10.3); δ_C (100MHz, $CDCl_3$) 157.8 (Ci), 150.8 (Ci), 142.6 (Ci), 141.5 (Ci, d, J_{C-P} 18.4), 137.9 (Ci), 136.8 (Ci), 132.6 (CH), 128.8-128.1 (CH), 127.3 (CH), 125.1 (Ci), 125.0 (CH), 124.8 (Ci, d, J_{C-P} 20.3), 123.5 (Ci, d, J_{C-P} 11.1), 122.6 (CH), 121.9 (Ci), 113.6 (CH), 89.8 (Ci), 72.9-72.1 (CH_2), 30.3 (CH_3), 29.4 (CH_3); δ_P (160MHz, $CDCl_3$) 28.395 (s); m/z (FAB) 676 (MH^+, 100%), 632 ($MH-CO_2^+$, 87), (Found: MH^+ 676.235791. $C_{42}H_{34}N_3O_4P$ requires MH, 676.236520).

(R_{3a},R_{7a})-1,3-(dimethyl)-2-(dibenzofuran diphenyl urethan-6-yl)-2,3,3a,4,5,6,7,7a-octahydro-1H-1,3,2-benzodiazaphosphole 2-oxide (**25**)



Dibenzofuran diphenyl urethane (**7e**) (1.0g, 2.56mmol) was suspended in ether (20.0ml) and TMEDA (1.16ml, 7.68mmol) added with stirring. The mixture was cooled to -78°C and s-BuLi (6.15ml, 7.68mmol of a 1.25M solution in cyclohexane) was added slowly dropwise. After stirring for 30min the dark red suspension was allowed to warm to room temperature and the mixture stirred for a further 3hrs. The suspension was then cooled to -78°C and the chloro diazaphospholidine oxide (**23**) (681mg, 3.07mmol) in THF (15.0ml) was added dropwise. After 45min the mixture was allowed to warm to room temperature and stirred for a further 16hrs. The reaction was quenched by the addition of a solution of ammonium chloride (10ml) and the aqueous phase extracted with DCM (3 x 20ml). The combined organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 0.5-5% MeOH/DCM followed by crystallisation from hot ethyl acetate gave (**25**) (928mg, 63%). mp. = 175-177°C (ethyl acetate); $[\alpha]^{20}_D$ = +32.4 (*c* = 1, $CHCl_3$); (Found: C, 68.47; H, 5.83; N, 6.90. $C_{34}H_{32}N_3O_4P$. H_2O requires C, 68.57; H, 5.71; N, 7.07%); ν_{max}($CHCl_3$ film)/cm^{-1} 3382 (NH), 1731 (C=O); δ_H (400MHz, $CDCl_3$) 10.59 (1H, bs, NH), 8.10 (1H, d, J 7.6), 7.64 (1H, dd, J 13.7, 7.3), 7.53 (1H, d, J 7.9), 7.43 (1H, td, J 7.3, 2.1), 7.35-7.20 (10H, m), 6.73 (1H, d, J 7.9), 3.00 (1H, m), 2.64 (4H, d, J 11.6), 2.38 (3H, d, J 11.9), 2.19 (1H, bd, J 11.6), 2.04-1.91 (3H, m), 1.45-1.24 (4H, m); δ_C (100MHz, $CDCl_3$) 158.3 (C*i*), 151.3 (C*i*), 142.9 (C*i*), 141.8 (C*i*), 131.6 (CH, d, J_{C-P} 5.5), 128.5 (CH, d, J_{C-P} 11.0), 128.2 (CH, d, J_{C-P} 5.5), 128.1 (CH), 124.8 (CH, d, J_{C-P} 9.2), 124.5 (C*i*), 123.2 (CH, d, J_{C-P} 11.0), 122.5 (CH), 122.3 (C*i*), 115.2 (Ci), 113.7 (C*i*), 113.4 (CH), 89.8 (C*i*), 64.6 (CH, d, J_{C-P} 7.3), 64.0 (CH, d, J_{C-P} 5.5), 28.8 (CH_3), 28.7 (CH_2), 28.3 (CH_2), 28.2 (CH_3), 27.9 (CH_2), 24.3 (CH_2); δ_P (160MHz, $CDCl_3$) 31.54 (s); m/z (thermospray) 578 (MH^+, 100%), 534 ($MH\text{-}CO_2^+$, 20). An X-ray grade crystal was prepared by slow evaporation from ethanol. See Appendix Chapter 3 for data.

NMR BINDING STUDIES

General Procedure for the Determination of Critical Association Constant for Hosts in $CDCl_3$ Solution

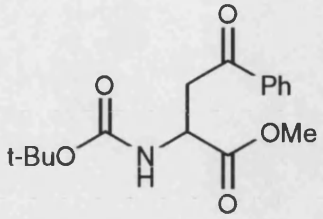
A $1.48x10^{-2}$M solution of **(24)** (azeotrope dried from $CHCl_3$) in dry $CDCl_3$ was taken as a starting concentration. A 1ml sample of this was subjected to ^1H NMR analysis (400MHz, 21-22°C) and the chemical shift of the carbamate NH noted. This sample was then diluted to half concentration and a 1ml sample analysed. This process was repeated until a constant, minimum value for the NH chemical shift was found. In this case the CAC was found to be at $1.85x10^{-3}$M.

General Procedure for the NMR Titration of Host-Guest Systems in $CDCl_3$ Solution

Stock solutions of **(25)** (azeotrope dried from $CHCl_3$) and N-Boc-Glycine were made in dry $CDCl_3$ under a nitrogen atmosphere. 1ml NMR samples were made up, under an atmosphere of nitrogen, such that the sample concentration remained at a constant value of $1.74x10^{-4}$M throughout. The ratio of guest (N-Boc-Glycine) to host was gradually increased across the sample range keeping the concentration of host at a constant. ^1H NMR analysis (400MHz, 21°C), following the chemical shift of the carbamate NH in the host, across the sample range was then carried out. ^{31}P NMR analysis (160MHz, 21°C) of the same set of samples was also carried out. The change in chemical shift was plotted against host/guest ratio and a value of the binding constant ($K\ M^{-1}$) calculated. In this case ^1H NMR gave K = $1031M^{-1}$ and ^{31}P NMR gave K = $819M^{-1}$ giving an average value of K = $930M^{-1}$.

APPLICATION OF DIAZAPHOSPHOLIDINE OXIDE RECEPTORS IN AMINO ACID SYNTHESIS

N-Boc-α-(1-oxo)-homophenylalanine methyl ester (**30**)



N-Boc-α-bromo glycine methyl ester (**29**) (100mg, 0.37mmol) was dissolved in THF (4.0ml). To this was added acetophenone-TMS-enol ether (176mg, 0.92mmol) followed by $ZnCl_2$ (59mg, 0.44mmol) in THF (4.0ml). The mixture was stirred at room temperature for 3hrs and then quenched by the addition of water. The aqueous phase was extracted into DCM (3 x 10ml), the combined organics were dried over sodium sulfate, filtered and solvent evaporated. Purification by column chromatography on silica eluted with 20% ethyl acetate/petrol gave (**30**) as a white foam (95mg, 84%). $\nu_{max}(CHCl_3$ film)/cm^{-1} 3441 (NH), 1746 (C=O), 1709 (C=O); δ_H (250MHz, $CDCl_3$) 7.96-7.92 (2H, m), 7.62-7.56 (1H, m), 7.50-7.44 (2H, m), 5.63 (1H, bd, J 8.4), 4.73-4.66 (1H, m), 3.8-3.68 (4H, m), 3.53 (1H, dd, J 18.0, 4.1) 1.44 (9H, s); δ_C (60MHz, $CDCl_3$) 197.6 (C*i*), 171.9 (C*i*), 155.4 (C*i*), 135.9 (C*i*), 133.5 (CH), 128.6 (CH), 128.0 (CH), 79.9 (C*i*), 52.5 (CH), 49.4 (CH_3), 40.8 (CH_2), 28.2 (CH_3); m/z (CI) 308 (MH^+, 30%), (Found: 308.1498. $C_{16}H_{21}NO_5$ requires MH, 308.1498).

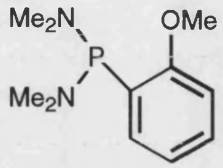
Host Catalysed Amino Acid Synthesis an Example Procedure

(**25**) (21mg, 0.037mmol) was dissolved in DCM (4.0ml) and N-Boc-α-bromo glycine methyl ester (**29**) (100mg, 0.37mmol) was added with stirring at room temperature, to this was added acetophenone-TMS-enol ether (0.19ml, 0.93mmol) and the mixture stirred for 48hrs. The reaction was quenched by the addition of ammonium chloride solution (5ml) and the aqueous extracted with DCM (3 x 10ml). The combined organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 20% ethyl acetate/petrol gave (**30**) as a colourless oil (27mg, 24%). Data consistent with that for N-Boc-α-(1-oxo)-homophenylalanine methyl ester (**30**) already described.

EXPERIMENTAL: SECTION 2

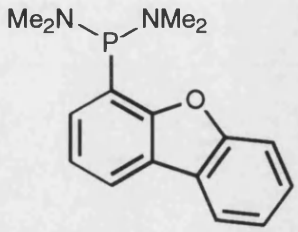
SYNTHESIS OF DIAZAPHOSPHOLIDINE LIGANDS

o-Anisyl-(bis-dimethylamino)-phosphine **(31a)**[11]



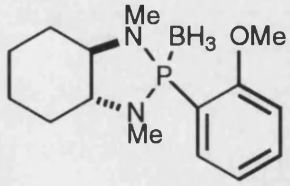
Anisole (5.0g, 46.3mmol) was dissolved in THF (30.0ml) and cooled to -78°C. n-BuLi (19.4ml, 48.6mmol of a 2.5M solution in hexanes) was added slowly, dropwise. The mixture was then allowed to warm to room temperature for 3hrs. Meanwhile PCl_3 (1.33ml, 15.3mmol) was cooled to 0°C and HMPT (5.56ml, 30.6mmol) was added slowly, dropwise. After the vigorous, fuming reaction had subsided the mixture was heated to 70°C for 30min. The colourless oil was allowed to cool to room temperature and diluted with THF (10.0ml). The lithiated anisole was recooled to -78°C and the solution of $ClP(NMe_2)_2$ added *via* cannular. The pale yellow solution was stirred at -78°C for 3hrs and then allowed to stir at room temperature overnight. The reaction was quenched by the addition of sodium bicarbonate solution and the aqueous phase extracted with DCM (3 x 50ml). The combined organics were dried over potassium carbonate, filtered and the solvent evaporated to give an orange oil. Purification by fractional distillation gave **(31a)** as a colourless oil (5.0g, 50%). δ_H (250MHz, $CDCl_3$) 7.38-7.33 (1H, m), 7.31-7.24 (1H, m), 7.00-6.93 (1H, m), 6.87-6.82 (1H, m), 3.83 (3H, s), 2.69-2.65 (12H, d, J 9.6); δ_P (160MHz, $CDCl_3$) 96.5 (s).

Dibenzofuran-4-(bis-dimethylamino)-phosphine **(31b)**



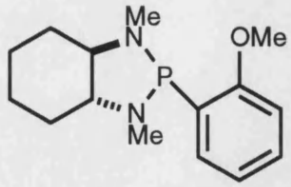
Dibenzofuran (2.0g, 11.9mmol) was dissolved in THF (10.0ml) and cooled to -78°C. n-BuLi (5.25ml, 12,5mmol of a 2.38M solution in hexanes) was added dropwise. The mixture was then allowed to warm to room temperature and stirred for 3hrs. Meanwhile PCl_3 (0.34ml, 3.93mmol) was cooled to 0°C and HMPT (1.43ml, 7.85mmol) was added slowly, dropwise. After the vigorous, fuming reaction had subsided the mixture was heated to 70°C for 30min. The colourless oil was allowed to cool to room temperature and diluted with THF (5.0ml). The lithiated dibenzofuran was recooled to -78°C and the solution of $ClP(NMe_2)_2$ added *via* cannular. The pale yellow solution was stirred at -78°C for 2hrs and then allowed to stir at room temperature overnight. The reaction was quenched by the addition of sodium bicarbonate solution and the aqueous phase extracted with ether (3 x 50ml). The combined organics were dried over potassium carbonate, filtered and the solvent evaporated to give an orange oil (3.63g, 107%). A portion (0.5g) of this oil was purified by flash chromatography on RP-18 silica eluted with 1% Et_3N/MeCN to give a colourless oil (361mg). ν_{max}(Liquid film)/cm^{-1} 1448 (P-Ar), 1058 (P-N); δ_H (250MHz, $CDCl_3$) 7.96-7.87 (2H, m), 7.58-7.32 (5H, m), 2.81 (12H, d, J 9.6); δ_C (60MHz, $CDCl_3$) 156.5 (C*i*), 156.0 (C*i*), 130.0 (CH), 126.7 (CH), 124.4 (C*i*), 123.9 (C*i*), 122.5 (CH), 122.3 (CH), 120.2 (CH), 120.1 (CH), 111.5 (CH), 41.5 (CH_3); δ_P (160MHz, $CDCl_3$) 92.45 (s); m/z (EI) 286 (M^+, 70%), (Found: 286.1235. $C_{16}H_{19}N_2OP$ requires M, 286.1235).

(R_{3a},R_{7a})-1,3-(dimethyl)-2-(o-anisyl)-2,3,3a,4,5,6,7,7a-octahydro-1H-1,3,2-benzodiazaphosphole P-borane Complex (**32**)



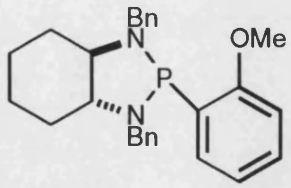
o-Anisyl-(bis-dimethylamino)-phosphine (**31a**) (220mg, 0.97mmol) was dissolved in toluene (2.0ml, degassed) and (R,R)-N,N'-dimethyl-1,2-diamino cyclohexane (**17**) (138mg, 0.97mmol) was added with stirring at room temperature. The mixture was heated to reflux, with an N_2 bubbler attached, for 32hrs, until the N_2 outflow was of neutral pH. The mixture was then allowed to cool to room temperature and BMS (0.15ml, 10M) was added dropwise. After 2hrs the reaction was quenched by the addition of sodium bicarbonate solution and the aqueous phase extracted with DCM (3 x 10ml). The combined organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 10% ethyl acetate/petrol gave (**32**) as a white solid (145mg, 50%). mp. 96-98°C (from ethyl acetate/hexane); $[\alpha]^{20}_D$ = + 6.3 (*c* = 1, $CHCl_3$); δ_H (250MHz, $CDCl_3$) 7.80-7.71 (1H, m), 7.47-7.42 (1H, m), 7.03-6.97 (1H, m), 6.94-6.89 (1H, dd, J 8.1, 4.4), 3.85 (3H, s), 2.60 (3H, d, J 12.5), 2.51 (2H, m), 2.45 (3H, d, J 13.7), 2.17 (1H, m), 2.04 (1H, m), 1.83 (2H, m), 1.28-1.23 (4H, m); δ_C (100MHz, $CDCl_3$) 161.1 (C*i*, d, J_{C-P} 5.0), 135.0 (CH, d, J_{C-P} 10.7), 133.3 (CH), 120.5 (C*i*), 120.2 (CH, d, J_{C-P} 9.4), 111.1 (CH, d, J_{C-P} 4.6), 67.5 (CH), 64.5 (CH), 55.3 (CH_3), 31.5 (CH_3, d, J_{C-P} 9.1), 29.3 (CH_3, d, J_{C-P} 2.9), 28.8 (CH_2, d, J_{C-P} 4.9), 28.3 (CH_2, d, J_{C-P} 8.1), 24.1 (CH_2), 24.0 (CH_2); δ_P (160MHz, $CDCl_3$) 107.2 (m); m/z (CI) 293 (MH^+, 23%), 279 ($MH\text{-}BH_3^+$, 90), (Found: 293.1954. $C_{15}H_{26}N_2OPB$ requires MH, 293.1954). An X-ray grade crystal was produced by slow dispersion of hexane into an ethyl acetate solution of (**32**) (see Appendix Chapter 4 for X-ray data).

(R_{3a},R_{7a})-1,3-(dimethyl)-2-(o-anisyl)-2,3,3a,4,5,6,7,7a-octahydro-1H-1,3,2-benzodiazaphosphole (**33a**)



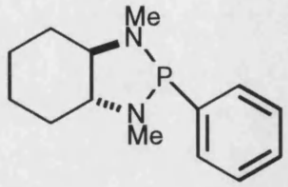
o-Anisyl-(bis-dimethylamino)-phosphine (**31a**) (160mg, 0.71mmol) was dissolved in toluene (2.0ml, degassed) and to this was added the (R,R)-N,N'-dimethyl-1,2-diamino cyclohexane (**17**) (100mg, 0.71mmol). The mixture was heated to reflux and stirred for 3 days. After this time the solvent was evaporated giving (**33a**) as pale cream crystals after drying under high vacuum (197mg, 100%). $[\alpha]^{20}_D$ = + 110 (*c* = 1.2, $CHCl_3$); ν_{max}(Liquid film)/cm^{-1} 2937 (Ar-OMe), 1461 (P-Ar), 1025 (P-N); δ_H (250MHz, $CDCl_3$) 7.56-7.52 (1H, m), 7.34-7.27 (1H, m), 6.99-6.93 (1H, m), 6.87-6.82 (1H, m), 3.85 (3H, s), 2.72 (3H, d, J 15.7), 2.36 (3H, d, J 15.4), 2.35-2.29 (1H, m), 2.23-2.17 (2H, m), 1.95-1.91 (1H, m), 1.82-1.74 (2H, m), 1.32-1.09 (4H, m); δ_C (100MHz, $CDCl_3$) 162.0 (C*i*, d, J_{C-P} 16.5), 132.5 (CH), 130.3 (CH), 127.5 (C*i*), 119.7 (CH), 109.7 (CH), 70.7 (CH, d, J_{C-P} 4.9), 65.7 (CH, d, J_{C-P} 9.1), 55.1 (CH_3), 37.0 (CH_3, d, J_{C-P} 37.6), 31.0 (CH_3, d, J_{C-P} 7.7), 30.1 (CH_2), 28.6 (CH_2, d, J_{C-P} 2.9), 24.4 (CH_2), 24.0 (CH_2); δ_P (160MHz, $CDCl_3$) 103.87 (s); m/z (EI) 278 (M^+, 45%), (Found: 278.1548. $C_{15}H_{23}N_2OP$ requires M, 278.1548).

(R_{3a},R_{7a})-1,3-(dibenzyl)-2-(o-anisyl)-2,3,3a,4,5,6,7,7a-octahydro-1H-1,3,2-benzodiazaphosphole (**33c**)



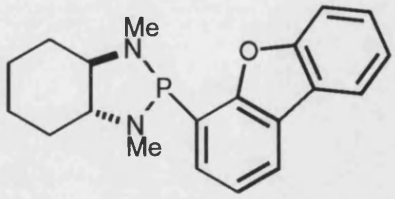
o-Anisyl-(bis-dimethylamino)-phosphine (**31a**) (112mg, 0.49mmol) was dissolved in toluene (2.0ml, degassed). To this was added (R,R)-N,N'-dibenzyl-1,2-diamino cyclohexane (144mg, 0.49mmol) and the mixture heated to reflux for 6 days. The solvent was then evaporated to give (**33c**) as a pale cream foam (210mg, 100%). $[\alpha]^{20}_D$ = + 58.5 (*c* = 1.3, $CHCl_3$); ν_{max}($CHCl_3$ film)/cm^{-1} 1461 (P-Ar), 1020 (P-N); δ_H (250MHz, $CDCl_3$) 7.71-7.66 (1H, m), 7.41-7.01 (11H, m), 6.99-6.96 (1H, m), 6.87-6.82 (1H,), 4.36-4.18 (4H, m), 3.70 (3H, s), 2.67-2.54 (2H, m), 1.74-1.62 (4H, m), 1.23-1.01 (4H, m); δ_C (100MHz, $CDCl_3$) 161.5 (C*i*, d, J_{C-P} 17.7), 142.2 (C*i*, d, J_{C-P} 8.9), 140.6 (C*i*), 140.5 (C*i*), 132.4 (CH), 130.1 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.3 (CH), 126.5 (CH), 126.0 (CH), 119.5 (CH), 109.7 (CH), 68.0 (CH, d, J_{C-P} 3.9), 66.0 (CH, d, J_{C-P} 7.9), 54.7 (CH_2, d, J_{C-P} 26.5), 54.9 (CH_3), 48.9 (CH_2, d, J_{C-P} 15.7), 31.0 (CH_2), 30.0 (CH_2), 24.4 (CH_2); δ_P (160MHz, $CDCl_3$) 103.36 (s); m/z (CI) 431 (MH+, 100%), (Found: 431.2252. $C_{27}H_{31}N_2OP$ requires MH, 431.2252).

(R_{3a},R_{7a})-1,3-(dimethyl)-2-(phenyl)-2,3,3a,4,5,6,7,7a-octahydro-1H-1,3,2-benzodiazaphosphole (**36**)



Phenyl (bis-dimethylamino) phosphine[9] (103mg, 0.53mmol) was dissolved in toluene (2.0ml, degassed) and the (R,R)-N,N'-dimethyl-1,2-diamino cyclohexane (**17**) (75mg, 0.53mmol) was added and the mixture heated to reflux for 2 days. The solvent was then evaporated to give (**36**) as a pale yellow oil (130mg, 100%). $[\alpha]^{20}_D$ = + 31.4 (*c* = 1.25, $CHCl_3$); ν_{max}(Liquid film)/cm^{-1} 1460 (P-Ar), 1024 (P-N); δ_H (250MHz, $CDCl_3$) 7.57-7.50 (2H, m), 7.40-7.33 (3H, m), 2.76 (3H, d, J 15.4), 2.21 (3H, d, J 15.7), 2.20-2.17 (2H, m), 1.92-1.74 (3H, m), 1.33-1.09 (5H, m); δ_C (60MHz, $CDCl_3$) 138.9 (C*i*, d, J_{C-P} 46.3), 131.0 (CH, d, J_{C-P} 19.6), 128.9 (CH), 127.3 (CH), 70.7 (CH, d, J_{C-P} 4.9), 65.3 (CH, d, J_{C-P} 7.9), 36.8 (CH_3, d, J_{C-P} 35.4), 30.6 (CH_3, d, J_{C-P} 8.8), 30.0 (CH_2), 28.6 (CH_2), 24.3 (CH_2), 23.9 (CH_2); δ_P (160MHz, $CDCl_3$) 111.74 (s); m/z (CI) 249 (MH^+, 71%), (Found: 249.1521. $C_{14}H_{21}N_2P$ requires MH, 249.15206).

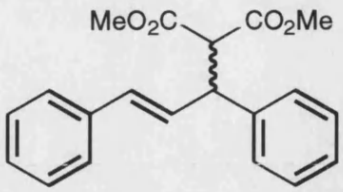
(R_{3a},R_{7a})-1,3-(dimethyl)-2-(dibenzofuran-4-yl)-2,3,3a,4,5,6,7,7a-octahydro-1H-1,3,2-benzodiazaphosphole (**37**)



Dibenzofuran-4-(bis-dimethylamino) phosphine (**31b**) (108mg, 0.37mmol) was dissolved in toluene (2.0ml degassed). To this was added the (R,R)-N,N'-dimethyl-1,2-diamino cyclohexane (**17**) (53mg, 0.37mmol) and the mixture heated to reflux for 3 days. The solvent was then evaporated to give (**37**) as a yellow oil (125mg, 100%). $[\alpha]^{20}_D$ = + 155.3 (*c* = 1.23, $CHCl_3$); ν_{max}(Liquid film)/cm^{-1} 1464 (P-Ar), 1025 (P-N); δ_H (400MHz, $CDCl_3$) 7.94-791 (2H, m), 7.66-7.61 (2H, m), 7.46-7.41 (1H, td, J 7.4, 1.4), 7.37-7.30 (1H, m), 7.24-7.22 (1H, m), 2.80 (3H, d, J 15.8), 2.46-2.38 (1H, m), 2.37 (3H, d, J 15.9), 2.31-2.23 (2H, m), 1.93-1.76 (3H, m), 1.40-1.14 (4H, m); δ_C (100MHz, $CDCl_3$) 156.0 (C*i*), 130.2 (CH, d, J_{C-P} 3.2), 128.9 (CH), 126.8 (CH), 125.2 (C*i*), 123.3 (C*i*), 122.5 (CH), 121.9 (C*i*), 121.3 (CH), 120.5 (CH), 111.7 (CH), 71.0 (CH, d, J_{C-P} 4.9), 66.2 (CH, d, J_{C-P} 9.6), 36.9 (CH_3), 30.8 (CH_3, d, J_{C-P} 8.1), 30.0 (CH_2), 28.6 (CH_2, d, J_{C-P} 3.2), 24.4 (CH_2), 24.0 (CH_2); δ_P (160MHz, $CDCl_3$) 102.4 (s); m/z (FAB) 339 (MH^+, 52%), sample decomposed before accurate mass analysis could be carried out.

ALLYLIC ALKYLATION REACTION

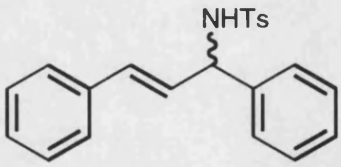
Palladium Catalysed Allylic Alkylation Reactions an Example Procedure



Ligand (**33a**) (89mg, 0.32mmol) was dissolved in DCM (0.5ml, degassed) to this was added palladium allyl chloride dimer (14.6mg, 0.04mmol) as a solution in DCM (0.5ml, degassed). The mixture was heated to 40°C for 2hrs then allowed to cool to room temperature 1,3-diphenyl-3-acetoxy-1-propene (**34**) (200mg, 0.79mmol) was then added as a solution in DCM (1.0ml, degassed) followed by dimethyl malonate (115mg, 0.87mmol), BSA (176mg, 0.87mmol) and sodium acetate (1mg). The resultant suspension was stirred at room temperature for 16hrs before diluting with ether and quenching with ammonium chloride solution. The aqueous phase was extracted with ether (3 x 10ml), the combined organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 10% ethyl acetate/petrol gave (**35**) as a colourless oil (294mg, 97%). δ_H (250MHz, $CDCl_3$) 7.33-7.19 (10H, m), 6.48 (1H, d, J 15.7), 6.31 (1H, dd, J 15.7, 8.1), 4.26 (1H, dd, J 10.8, 8.1), 3.95 (1H, d, J 11.0), 3.70 (3H, s), 3.52 (3H, s). Agrees with literature values.[86] Enantiomeric excess was determined to be 89% (R) by chiral shift NMR using (+)-Eu(HFC)$_3$. A sample of (**35**) of known mass (approx. 20mg) was dissolved in $CDCl_3$ (1.0ml). This solution was then added to a sample vial containing 4-4.5 equivalents of (+)-Eu(hfc)$_3$ and shaken for a few seconds until a bright yellow solution had formed. NMR analysis of this sample (250MHz) gave 4 sharp signals in the region of 4.0ppm. The ratio of signal 1 (4.24ppm) and signal 2 (4.13ppm) gave a measure of the enantioselectivity. Signal 1 was the major peak corresponding to the (R)-enantiomer in this system.[86]

ALLYLIC AMINATION REACTION

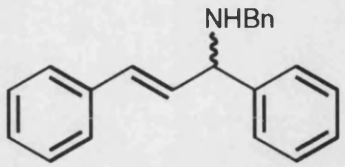
Palladium Catalysed Allylic Amination Reactions an Example Procedure



Tosyl amide (137mg, 0.8mmol) was added slowly to a suspension of sodium hydride (32mg, 0.8mmol) in THF (4.0ml). The mixture was allowed to stir at room temperature for 2hrs and then the solvent removed under reduced pressure and the sodium salt (**42**) resuspended in DCM (2.0ml, degassed). In the mean time ligand (**33a**) (22.2mg, 0.08mmol) was dissolved in DCM (0.5ml degassed) and to this was added solid palladium allyl chloride dimer (7.3mg, 0.02mmol). The mixture was heated to 40°C for 1.5hrs and then allowed to cool to room temperature. 1,3-diphenyl-3-acetoxy-1-propene (100mg, 0.4mmol) was then added as a solution in DCM (0.5ml degassed) followed by the suspension of tosyl amide sodium salt and sodium acetate (1mg). The mixture was stirred at room temperature for 64hrs and then quenched by the addition of ether and ammonium chloride solution. The aqueous phase was extracted with ether (3 x 10ml) and the combined organics dried over sodium sulfate, filtered and solvent evaporated. Purification by flash chromatography on silica eluted with 15% ethyl acetate/petrol gave (**43**) as a white solid (65mg, 45%). $[\alpha]^{20}_D$ = + 26.5 (*c* = 0.8, $CHCl_3$); δ_H (250MHz, $CDCl_3$) 7.65 (2H, d, J 8.4), 7.26-7.13 (12H, m), 6.36 (1H, d, J 16.0), 6.07 (1H, dd, J 15.7, 6.7), 5.11 (1H, t, J 7.0), 4.89 (1H, d, J 7.3), 2.32 (3H, s). Agrees with literature values.[106] Enantiomeric excess was determined by chiral HPLC using a Chiralcel OD column, 75:25 Hexane/IPA, 0.5ml/min, 254nm. ee = 75.6% (S), (+)-(S)-isomer t_r = 22.49min, (-)-(R)-isomer t_r = 15.94min.

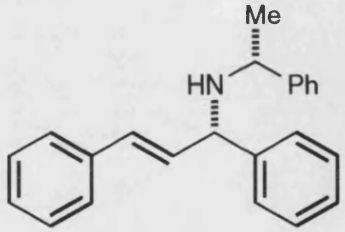
The following were prepared according to the procedure described for N-(1,3-diphenyl-1-propenyl)-*p*-tolyl sulfonamide (**43**).

N-(1,3-diphenyl -1-propenyl)-benzylamine (**39**)[106, 107]



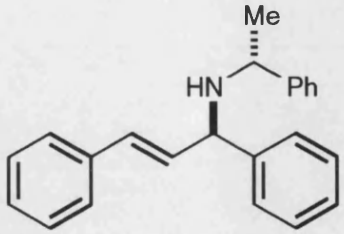
Amine (**39**) was formed as a colourless oil in 68% yield. $[\alpha]^{20}_D$ = + 27.4 (*c* = 1.5, $CHCl_3$); δ_H (250MHz, $CDCl_3$) 7.45-7.19 (15H, m), 6.58 (1H, d, J 15.7), 6.31 (1H, dd, J 16.0, 7.6), 4.39 (1H, d, J 7.3), 3.77 (2H, d, J 1.5), 2.0 (1H, bs, NH). Agrees with literature values. Enantiomeric excess determined by chiral HPLC using a Chiralcel OD column, 200:1 Hexane/IPA, 0.5ml/min, 254nm, ee = 78.1% (S), (+)-(S)-isomer t_r = 36.58min, (-)-(R)-isomer t_r = 34.37min.

(+)-(S)-N-(1,3-diphenyl -1-propenyl)-(R)-α-methyl benzylamine (**41**) Major isomer[119]



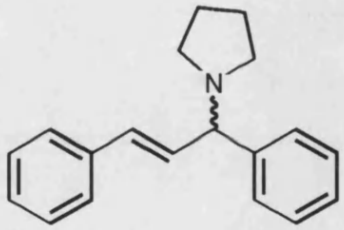
Amine (**41**) was formed as a colourless oil in 67% yield as a mixture of diastereomers. $[\alpha]^{20}_D$ = + 78.3 (*c* = 1.0, $CHCl_3$); ν_{max}($CHCl_3$ film)/cm^{-1} 3423 (NH), 1637 (C=C); δ_H (250MHz, $CDCl_3$) 7.40-7.21 (15H, m), 6.41 (1H, d, J 16.0), 6.24 (1H, dd, J 16.0, 7.9), 4.16 (1H, d, J 7.9), 3.90 (1H, q, J 6.7), 1.75 (1H, bs, NH), 1.39 (3H, d, J 6.7); δ_C (60MHz, $CDCl_3$) 145.5 (C*i*), 143.2 (C*i*), 136.9 (C*i*), 131.9 (CH), 130.9 (CH), 128.4 (CH), 127.3 (CH), 127.0 (CH), 126.8 (CH), 126.6 (CH), 126.3 (CH), 61.9 (CH), 54.9 (CH), 24.4 (CH_3).

(-)-(R)-N-(1,3-diphenyl -1-propenyl)-(R)-α–methyl benzylamine (**41**) Minor isomer[119]



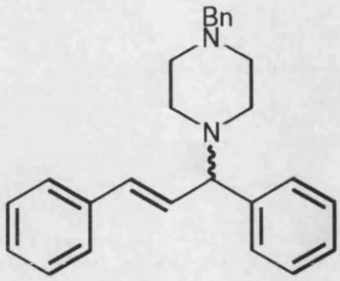
$[\alpha]^{20}_D$ = - 8.5 (*c* = 1.45, $CHCl_3$); ν_{max}($CHCl_3$ film)/cm^{-1} 3422 (NH), 1654 (C=C); δ_H (250MHz, $CDCl_3$) 7.33-7.24 (15H, m), 6.45 (1H, d, J 16.0), 6.26 (1H, dd, J 16.0, 7.8), 4.17 (1H, d, J 7.8), 3.65 (1H, q, J 6.7), 1.73 (1H, bs, NH), 1.33 (3H, d, 6.7); δ_C (60MHz, $CDCl_3$) 145.5 (C*i*), 142.8 (C*i*), 136.9 (C*i*), 133.1 (CH), 129.4 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 126.8 (CH), 126.6 (CH), 126.3 (CH) 62.1 (CH), 54.7 (CH), 24.5 (CH_3).

(+)-(S)-N-(1,3-diphenyl -1-propenyl) pyrrolidine (**45**)



Amine (**45**) was formed as a pale cream solid in 48% yield. $[\alpha]^{20}_D$ = + 2.9 (*c.* = 1.0, $CHCl_3$); ν_{max}($CHCl_3$ film)/cm^{-1} 2967, 2791, 1492, 1451, 1135, 965; δ_H (250MHz, $CDCl_3$) 7.44-7.18 (10H, m), 6.56 (1H, d, J 15.7), 6.41 (1H, dd, J 15.7, 8.1), 3.76 (1H, d, J 8.4), 2.58-2.41 (4H, m), 1.80-1.75 (4H, m); δ_C (100MHz, $CDCl_3$) 143.0 (C*i*), 136.9 (C*i*), 133.0 (CH), 129.7 (CH), 128.5 (CH), 128.3 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 126.3 (CH), 74.3 (CH), 53.0 (CH_2), 23.2 (CH_2); m/z (EI) 263 (M^+, 40%), (Found: 263.1674. $C_{19}H_{21}N$ requires M, 263.1674); HPLC (Chiralcel OD, 200:1 Hexane/IPA, 0.5 ml/min, 254nm) ee = 67.8% (S), (+)-(S)-isomer t_r = 11.72 min, (-)-(R)-isomer t_r = 10.49 min.

(+)-(S)-N-(1,3-diphenyl -1-propenyl)-N'-benzyl piperazine **(47)**



Amine (**47**) was formed as a white solid in 63% yield. $[\alpha]^{20}_D$ = + 15.4 (*c* = 1.0, $CHCl_3$); ν_{max}($CHCl_3$ film)/cm^{-1} 2938, 2813, 1637, 1494, 1452, 1136, 1004, 967; δ_H (250MHz, $CDCl_3$) 7.40-7.18 (15H, m), 6.54 (1H, d, J 15.7), 6.30 (1H, dd, J 16.0, 8.7), 3.81 (1H, d, J 8.7), 3.51 (2H, s), 2.46 (8H, m); δ_C (100MHz, $CDCl_3$) 141.7 (C*i*), 137.8 (C*i*), 136.7 (C*i*), 131.5 (CH), 131.0 (CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.3 (CH), 127.0 (CH), 126.8 (CH), 126.2 (CH), 74.1 (CH), 62.9 (CH_2), 53.0 (CH_2), 51.3 (CH_2); m/z (CI) 369 (MH^+, 15%), (Found: 369.2331 $C_{26}H_{28}N_2$ requires MH, 369.23307); HPLC (Chiralcel OD, 200:1 Hexane/IPA, 0.4 ml/min, 254nm) ee = 58.3% (S), (+)-(S)-isomer t_r = 25.70 min, (-)-(R)-isomer t_r = 28.05 min.

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Appendix

APPENDIX:

CHAPTER 1: MOLECULAR MODELLING STUDIES

The modelling carried out in this project made use of the MacroModel programme developed by Clarke Still and co-workers at Columbia University.[1] This programme utilises Molecular Mechanics to enable rapid calculation of free energies with a fair degree of accuracy. The program can provide information about the relative free energies of populated, low energy conformations for hosts and host-guest complexes both in gas phase and solution. Different force fields are available which are best suited to certain types of molecule (Amber* is used for peptides). These force fields provide a more accurate description of the types of bonding present in such molecules. Special functions such as MonteCarlo searches enable an assessment of intermolecular interactions between host and guest to be made.

Molecular Mechanics

Molecular Mechanics assumes that the energy of a molecular system comprises of five additive and non-interacting terms:

1) The sum of all diatomic bond stretches
2) The sum of all triatomic bond angle deformations
3) The sum of all tetraatomic bond torsions
4) The sum of all non-bonded Van der Waals repulsions
5) The sum of all electrostatic attractions of individual bond dipoles

Each of the above can be expressed in terms of simple mathematical equations which can be solved quickly on the computational time scale provided the appropriate parameters are available. Terms 1-3 account for the strain in the system, term 4 accounts for steric repulsions and term 5 for hydrogen bonding and dipole interactions. The modelling program takes the relevant information and attempts to minimise the total energy of the system by adjusting the above parameters for all possible degrees of freedom within the molecule.

There are however limitations in this approach. Molecular Mechanics does not deal well with Van der Waals and electrostatic interactions due to anisotropy and polarisability effects which are difficult to predict. Properties which are dependent on the electron distribution within the molecule are best modelled by quantum mechanical methods such as molecular orbital theory.

MonteCarlo Searches

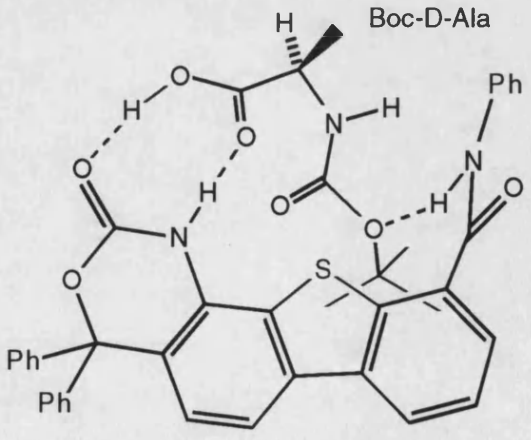
The MonteCarlo approach enables the modelling of host-guest systems where a minimum energy conformation of the host-guest complex is desired. The search is carried out in a manner which avoids the restriction of the complex at a local minimum and (providing enough steps are included) finds the absolute minimum of the system. This is achieved by the following process:

Starting with a minimised structure where host and guest are placed in an appropriate docking orientation the computer generates changes in the torsional angles of both host and guest as well as the translational and rotational position of the host relative to guest within a defined energy range. The number of such changes made can be adjusted to ensure that all the possible conformations are found in their statistical energy distribution. After each change the structure found is minimised to a defined degree of accuracy so that the relative energies of different structures can be compared. As with the simpler conformational searches the MonteCarlo search can be carried out for systems in vacuum or in solvent. The latter providing a more accurate picture of the molecular system.

Docking Studies Carried Out on Cleft Receptor (**8b**)

Separate conformational searches using the Macromodel Amber* force field were carried out on cleft receptor (**8b**) and N-Boc protected D-alanine to find the minimum energy conformations for each in the unbound state (vacuum phase). These minimum energy structures were then combined in a MonteCarlo search (again using Amber*) to find the lowest energy bound system (see fig. 1). The results were discussed in some detail in Section 1 Chapter 1.

Fig. 1:

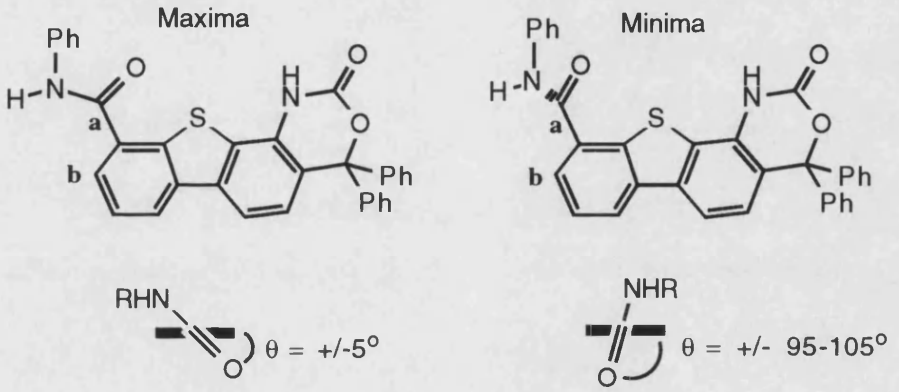


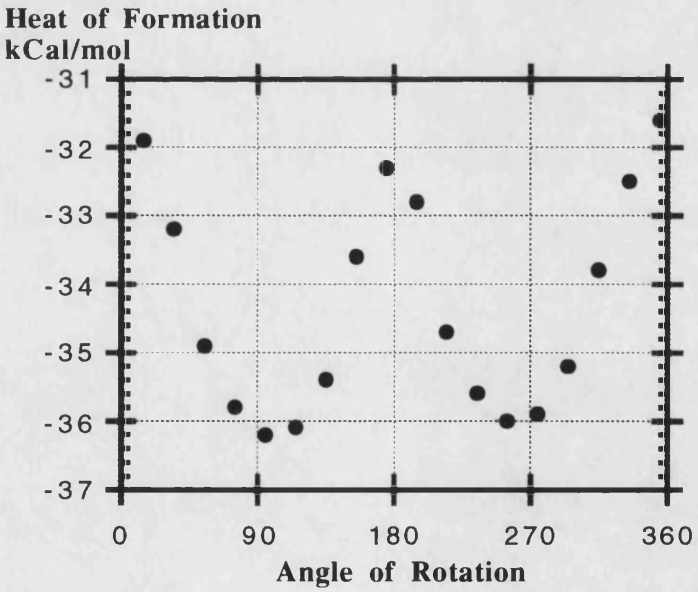
Receptor (**8b**)

Studies on the Rotation of the Amide Side Chain

The ability of the amide to rotate was studied using a semi empirical approach with the MOPAC program using PM3parameters. The amide was allowed to rotate about the aryl-carbonyl bond **a** (as shown in fig. 2) and the change in heat of formation measured. A plot of dihedral angle against heat of formation (see graph) shows which orientations of the amide lead to low and high energies. Not surprisingly the lowest energy structures correspond to the structures where the amide is out of plane, with the carbonyl pointing away from the C-S bond to minimise any dipolar interactions.

Fig. 2:

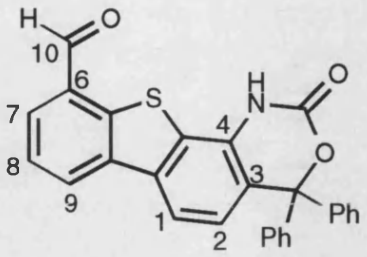




1) F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Canfield, G. Chang, T. Hendrickson, W. C. Still, *J. Comp. Chem.*, 1990, **11**, 440.

APPENDIX:

CHAPTER 2: COSY AND NOESY SPECTRA OF (8a)



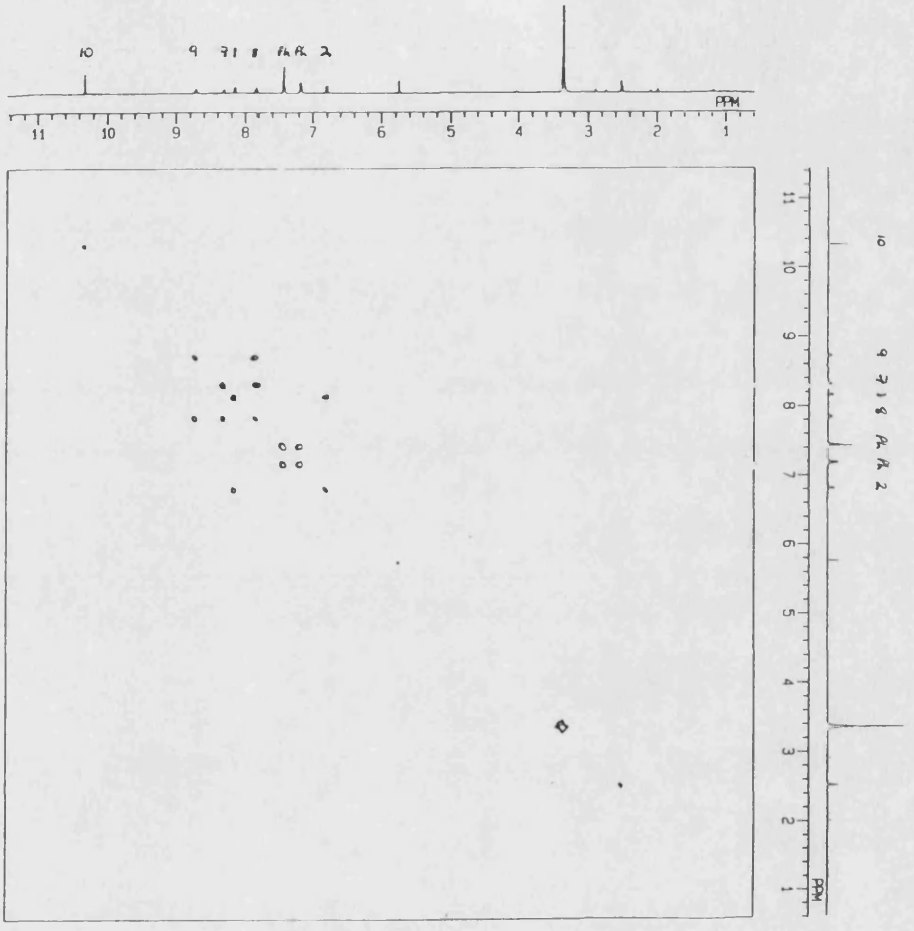
^{1}H-^{1}H COSY

Signals were assigned as shown in the table below.

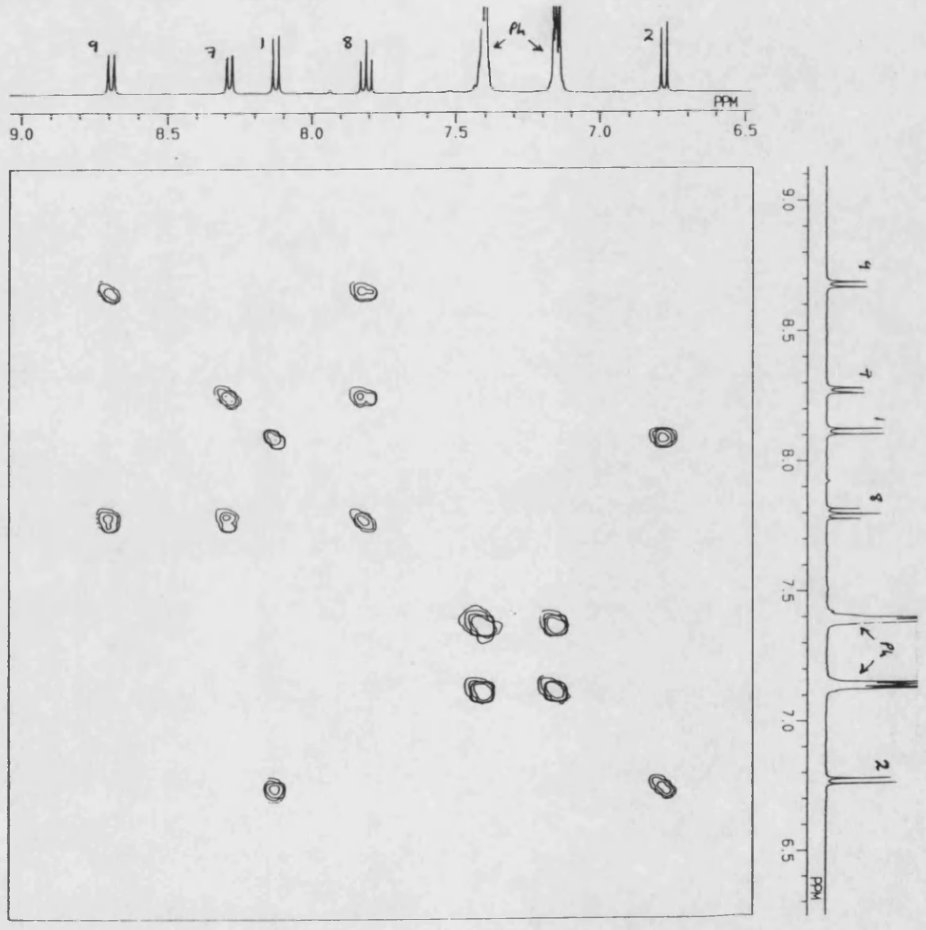
Proton No.	Signal (ppm)	Multiplicity	J (Hz)	COSY
1	8.15	d	8.3	1-2
2	6.80	d	7.8	2-1
7	8.30	dd	7.3, 1.5	7-8
8	7.83	t	7.8	8-7, 8-9
9	8.71	dd	7.8, 1.0	9-8
10	10.32	s	-	-

COSY interactions are shown in the following spectra.

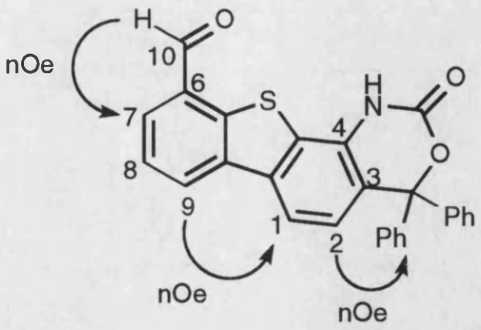
^{1}H-^{1}H COSY (DMSO-d6)



^{1}H-^{1}H-COSY (DMSO-d6) Expansion

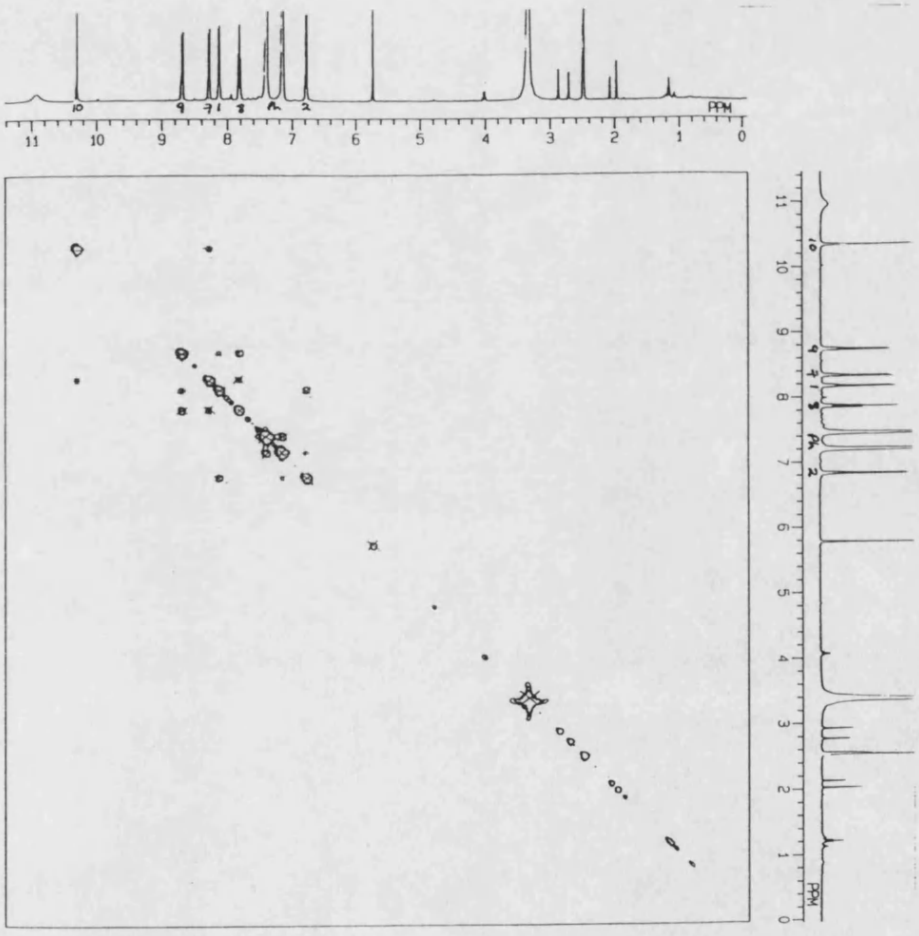


NOESY Data

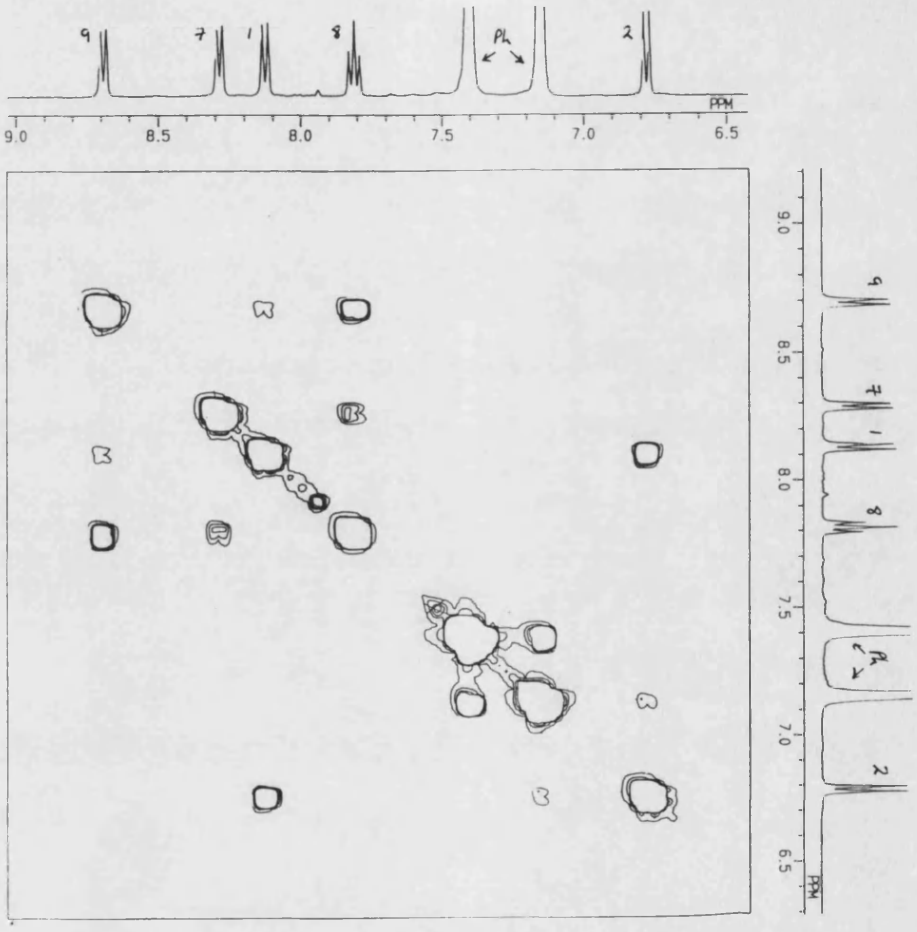


The following spectra clearly show nOe interactions between the pairs of signals (10-7, 9-1, 2-Ph).

NOESY (DMSO-d6)

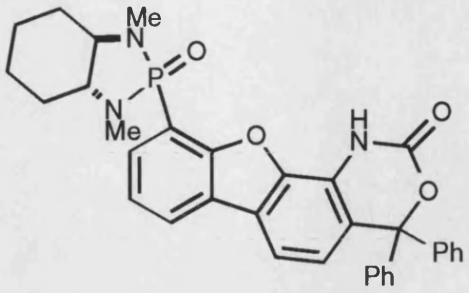


NOESY (DMSO-d6) Expansion



APPENDIX:

CHAPTER 3: X-RAY STRUCTURE OF DIAZAPHOSPHOLIDINE OXIDE (25)



A crystal of approximate dimensions 0.06 x 0.06 x 0.03 mm was used for data collection.

Crystal Data

$C_{34}H_{34}N_3O_5P$, M = 595.61, Monoclinic, a = 37.702(4), b = 13.057(2), c = 12.481(2) Å, α = 90, β = 93.61(1), γ = 90°, U = 6131.9(15) Å^3, space group C2, Z = 8, D_c = 1.290 gcm^{-3}, (μMo-K$_\alpha$) = 0.136 mm^{-1}, F(000) = 2512.

Crystallographic measurements were made at 293(2)° K, on a CAD4 automatic four-circle diffractometer in the range 2.01<θ<23.9(2)°. Data (5120 reflections) were corrected for Lorentz and polarisation but not for absorption.

The asymmetric unit contains two molecules of the parent compound which differ very slightly in the conformation of the cyclohexyl rings, and two water molecules.

In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant except for H3 and H61 (attached toN3 and N61 respectively) and the water protons H51, H52, H101 and H102 (attached in respective pairs to O5 and O10). These protons were located in the penultimate difference Fourier electron-density map and refined at a distance of 0.98 Å from the relevant parent atoms.

Examination of the supramolecular structure revealed that neighbouring pairs of molecules are involved in an interesting hydrogen bonding array with the two water molecules acting as a lattice 'cement'. Typically, O1 of the asymmetric unit as presented interacts with H101 and H52 while H3 hydrogen bonds to O10. [O1-H101, 1.92(3); O1-H52, 1.82(2); H3-O10, 1.78(2) Å]. Similarly, O6 has an affinity for H102 and H51 of the water molecule generated by the symmetry operator *-0.5+x, -0.5+y, z*, and H61 bonds to O5 of the water molecule

generated by this same transformation. [O6-H102, 1.81(2); O6-H51, 1.95(1); H61-O5, 1.79(2) Å].

It should be noted that although the residual values for this structure are quite good they do not reflect the fact that the esd values are relatively high. More data would have been desirable, but the crystal size was fairly large. A more significant contributory factor to these high esds is perhaps that this structure is pseudo-centrosymmetric. The statistics were centrosymmetric and it was possible to both solve and anisotropically refine the structure in space group *C2/c*. This refinement was found to effectively average the cyclohexyl rings as a planar six membered ring! The space group *C2/c* did incur a number of systematic absence violations associated with the inherent glide plane, but the intensity of these reflections was weak in comparison with the data set at large.

The solution of the structure (SHELX86)[1] and refinement (SHELX93)[2] converged to a conventional [i.e. based on 3533 with Fo>4σ(Fo)] *R1* = 0.0418 and *wR2* = 0.1189. Goodness of fit = 1.147. The max. and min. residual densities were 0.265 and -0.219 eÅ^{-3} respectively. The molecule of (**25**) present in the asymmetric unit is shown in Section 1 Chapter 4 Fig. 1.19, along with the labelling scheme used. The plots were produced using ORTEX[3]. Final fractional atomic coordinates and isotropic thermal parameters, bond distances and angles are given in Tables 2 and 3 respectively. Table 4 gives anisotropic displacement factors and Table 5 shows hydrogen coordinates and the corresponding isotropic displacement factors.

1) Sheldrick G. M., Acta Cryst., A46, 467-73, 1990.
2) Sheldrick G. M., J. Appl. Cryst., 1995 (In preparation).
3) McArdle P., J. Appl. Cryst., 27, 438, 1994.

Table 1: Crystal Data and Structure Refinement for (25)

Empirical formula	$C_{34}H_{34}N_3O_5P$
Formula weight	595.61
Temperature	293(2)° K
Wavelength	0.70930 Å
Crystal system	Monoclinic
Space group	C2
Unit cell dimensions	a = 37.702(4)Å
	b = 13.057(2)Å beta = 93.61 (1)°
	c = 12.481(2)Å
Volume	6132(2) $Å^3$
Z	8
Density (calculated)	1.290 Mg/m^3
Absorption coefficient	0.136 mm^{-1}
F(000)	2512
Crystal size	0.06 x 0.06 x 0.03 mm
Theta range for data collection	2.01 to 23.92°.
Index ranges	0<=h<=43; 0<=k<=14; -14<=l<=14
Reflections collected	5120
Independent reflections	5033 [R(int) = 0.0283]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5030 / 7 / 798
Goodness-of-fit on F^2	1.147
Final R indices [$I>2\sigma(I)$]	R1 = 0.0418 wR2 = 0.1189
R indices (all data)	R1 = 0.0829 wR2 = 0.1447
Absolute structure parameter	0(2)
Largest diff. peak and hole	0.266 and -0.213 $eÅ^3$
Weighting scheme	calc $w=1/[\sigma^2(Fo^2)+(0.0813P)^2+2.4440P]$
	where $P=(Fo^2+2Fc^2)/3$
Extinction coefficient	0.0018(34)

Table 2: Atomic Coordinates ($x10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 x 10^3$) for (25). Ueq is defined as one third of the trace of the Uij tensor.

Atom	x	y	z	U(eq)
P(1)	-2344(5)	-3610(19)	-4844(16)	42(6)
N(1)	-2246(18)	-4491(59)	-3905(51)	47(17)
N(2)	-1966(20)	-2996(64)	-4650(56)	50(20)
N(3)	-3657(19)	-4887(64)	-7005(56)	48(20)
O(1)	-2440(15)	-3954(59)	-5953(44)	59(19)
O(2)	-3185(13)	-3682(51)	-5565(40)	44(14)
O(3)	-4211(14)	-4924(57)	-7927(40)	56(18)
O(4)	-3756(17)	-5704(78)	-8591(50)	84(25)
O(5)	-2091(15)	-4040(52)	-7852(44)	50(16)
C(1)	-1856(22)	-4513(77)	-3692(67)	49(22)
C(2)	-1722(25)	-5018(105)	-2656(79)	78(35)
C(3)	-1315(28)	-4927(121)	-2589(100)	95(45)
C(4)	-1199(25)	-3815(129)	-2690(82)	88(44)
C(5)	-1357(21)	-3280(87)	-3716(70)	61(27)
C(6)	-1756(20)	-3399(72)	-3720(64)	47(22)
C(7)	-2713(22)	-2885(74)	-4380(60)	41(21)
C(8)	-2658(24)	-2163(76)	-3566(61)	46(23)
C(9)	-2929(24)	-1588(82)	-3174(72)	56(25)
C(10)	-3278(24)	-1702(74)	-3598(68)	52(24)
C(11)	-3346(22)	-2410(70)	-4409(62)	41(21)
C(12)	-3066(23)	-2981(70)	-4780(60)	40(22)
C(13)	-3551(20)	-3556(79)	-5661(57)	41(21)
C(14)	-3666(22)	-2793(71)	-4996(61)	41(20)
C(15)	-4027(23)	-2590(79)	-4971(66)	51(25)
C(16)	-4260(24)	-3184(78)	-5624(68)	49(25)
C(17)	-4140(21)	-3948(72)	-6282(59)	41(21)
C(18)	-3778(21)	-4138(74)	-6331(58)	41(22)
C(19)	-4378(22)	-4702(86)	-6913(63)	49(25)
C(20)	-3866(24)	-5212(84)	-7876(68)	52(25)
C(21)	-4738(22)	-4259(83)	-7267(65)	49(25)
C(22)	-5027(24)	-4396(89)	-6665(71)	60(28)
C(23)	-5354(25)	-3974(98)	-6964(83)	65(30)
C(24)	-5394(31)	-3402(114)	-7869(99)	84(40)
C(25)	-5112(33)	-3261(147)	-8482(100)	114(60)
C(26)	-4784(30)	-3681(127)	-8183(88)	89(41)
C(27)	-4413(22)	-5734(84)	-6334(65)	49(23)
C(28)	-4575(28)	-6555(91)	-6868(90)	62(29)
C(29)	-4614(30)	-7476(99)	-6379(98)	75(33)
C(30)	-4498(31)	-7628(102)	-5331(104)	78(33)
C(31)	-4338(31)	-6827(111)	-4776(91)	81(36)
C(32)	-4296(27)	-5879(90)	-5266(75)	61(27)

C(33)	-2439(28)	-5453(84)	-3970(85)	69(30)
C(34)	-1868(25)	-2071(82)	-5194(76)	60(27)
P(2)	-7683(6)	-10768(18)	-9978(16)	41(6)
N(4)	-8044(18)	-11423(60)	-10308(54)	44(18)
N(5)	-7793(16)	-9776(56)	-10731(48)	44(17)
N(6)	-6367(19)	-9327(65)	-7995(55)	47(20)
O(6)	-7585(15)	-10534(56)	-8841(42)	53(17)
O(7)	-6840(13)	-10596(46)	-9403(39)	39(14)
O(8)	-5814(14)	-9260(54)	-7101(37)	54(17)
O(9)	-6270(16)	-8456(69)	-6441(49)	74(22)
O(10)	-2946(16)	-5317(53)	-7002(43)	51(16)
C(35)	-8311(21)	-10774(78)	-10900(60)	46(20)
C(36)	-8577(25)	-11311(94)	-11658(77)	71(30)
C(37)	-8809(30)	-10488(115)	-12208(97)	95(46)
C(38)	-8597(31)	-9655(119)	-12755(92)	100(46)
C(39)	-8309(26)	-9181(85)	-11985(84)	69(29)
C(40)	-8086(20)	-10048(72)	-11515(61)	46(22)
C(41)	-7315(22)	-11464(70)	-10502(59)	39(20)
C(42)	-7373(26)	-12209(77)	-11290(66)	51(24)
C(43)	-7094(27)	-12769(79)	-11696(70)	57(25)
C(44)	-6749(25)	-12621(76)	-11318(69)	55(25)
C(45)	-6679(23)	-11869(70)	-10532(63)	43(22)
C(46)	-6959(22)	-11324(67)	-10150(61)	38(20)
C(47)	-6475(19)	-10701(76)	-9317(56)	37(20)
C(48)	-6359(22)	-11468(74)	-9992(60)	41(21)
C(49)	-5993(24)	-11647(78)	-9998(67)	50(24)
C(50)	-5766(24)	-11042(77)	-9375(67)	48(24)
C(51)	-5887(22)	-10257(75)	-8727(60)	43(21)
C(52)	-6247(22)	-10088(75)	-8672(59)	42(22)
C(53)	-5649(21)	-9501(78)	-8109(60)	42(21)
C(54)	-6161(23)	-8959(84)	-7143(66)	52(25)
C(55)	-5611(21)	-8495(79)	-8703(65)	46(23)
C(56)	-5720(26)	-8370(87)	-9782(70)	58(28)
C(57)	-5678(30)	-7445(96)	-10284(77)	70(31)
C(58)	-5526(32)	-6630(102)	-9761(98)	78(33)
C(59)	-5413(28)	-6723(93)	-8697(94)	70(31)
C(60)	-5458(26)	-7653(92)	-8166(83)	59(29)
C(61)	-5287(23)	-9960(80)	-7747(67)	48(24)
C(62)	-5243(29)	-10563(120)	-6838(89)	90(43)
C(63)	-4919(33)	-10991(146)	-6553(108)	116(61)
C(64)	-4636(31)	-10889(126)	-7160(103)	89(41)
C(65)	-4676(27)	-10296(98)	-8057(88)	69(32)
C(66)	-4996(24)	-9826(85)	-8351(70)	55(25)
C(67)	-8173(25)	-12231(76)	-9613(80)	62(27)
C(68)	-7536(25)	-9000(88)	-11022(81)	64(28)

Table 3: Bond Lengths [Å] and Angles [°] for (25)

P(1)-O(1)	1.48(6)	O(3)-C(19)-C(17)	108(7)
P(1)-N(2)	1.64(8)	C(21)-C(19)-C(17)	113(9)
P(1)-N(1)	1.67(7)	O(3)-C(19)-C(27)	107(8)
P(1)-C(7)	1.81(9)	C(21)-C(19)-C(27)	112(7)
N(1)-C(33)	1.45(12)	C(17)-C(19)-C(27)	113(7)
N(1)-C(1)	1.48(10)	O(4)-C(20)-O(3)	120(8)
N(2)-C(34)	1.45(12)	O(4)-C(20)-N(3)	123(9)
N(2)-C(6)	1.46(10)	O(3)-C(20)-N(3)	117(8)
N(3)-C(20)	1.37(11)	C(26)-C(21)-C(22)	118(9)
N(3)-C(18)	1.39(11)	C(26)-C(21)-C(19)	121(8)
O(2)-C(13)	1.39(9)	C(22)-C(21)-C(19)	121(8)
O(2)-C(12)	1.39(10)	C(21)-C(22)-C(23)	122(9)
O(3)-C(20)	1.35(10)	C(24)-C(23)-C(22)	120(10)
O(3)-C(19)	1.48(9)	C(23)-C(24)-C(25)	120(10)
O(4)-C(20)	1.20(10)	C(24)-C(25)-C(26)	121(10)
C(1)-C(6)	1.50(13)	C(21)-C(26)-C(25)	120(10)
C(1)-C(2)	1.51(12)	C(28)-C(27)-C(32)	117(10)
C(2)-C(3)	1.54(14)	C(28)-C(27)-C(19)	120(8)
C(3)-C(4)	1.5(2)	C(32)-C(27)-C(19)	123(9)
C(4)-C(5)	1.54(13)	C(29)-C(28)-C(27)	122(10)
C(5)-C(6)	1.51(11)	C(28)-C(29)-C(30)	121(10)
C(7)-C(8)	1.39(12)	C(29)-C(30)-C(31)	118(10)
C(7)-C(12)	1.40(11)	C(30)-C(31)-C(32)	121(10)
C(8)-C(9)	1.38(13)	C(27)-C(32)-C(31)	120(10)
C(9)-C(10)	1.39(12)	O(6)-P(2)-N(5)	115(4)
C(10)-C(11)	1.38(12)	O(6)-P(2)-N(4)	120(4)
C(11)-C(12)	1.40(12)	N(5)-P(2)-N(4)	95(4)
C(11)-C(14)	1.46(12)	O(6)-P(2)-C(41)	107(4)
C(13)-C(14)	1.38(12)	N(5)-P(2)-C(41)	111(4)
C(13)-C(18)	1.39(11)	N(4)-P(2)-C(41)	107(4)
C(14)-C(15)	1.39(11)	C(67)-N(4)-C(35)	118(7)
C(15)-C(16)	1.40(13)	C(67)-N(4)-P(2)	122(6)
C(16)-C(17)	1.38(12)	C(35)-N(4)-P(2)	111(6)
C(17)-C(18)	1.39(10)	C(68)-N(5)-C(40)	119(7)
C(17)-C(19)	1.52(13)	C(68)-N(5)-P(2)	123(6)
C(19)-C(21)	1.52(13)	C(40)-N(5)-P(2)	110(6)
C(19)-C(27)	1.5(2)	C(54)-N(6)-C(52)	122(8)
C(21)-C(26)	1.37(14)	C(47)-O(7)-C(46)	105(6)
C(21)-C(22)	1.37(12)	C(54)-O(8)-C(53)	119(6)
C(22)-C(23)	1.38(13)	N(4)-C(35)-C(36)	117(8)
C(23)-C(24)	1.4(2)	N(4)-C(35)-C(40)	103(6)
C(24)-C(25)	1.4(2)	C(36)-C(35)-C(40)	110(7)
C(25)-C(26)	1.4(2)	C(35)-C(36)-C(37)	107(9)
C(27)-C(28)	1.38(14)	C(36)-C(37)-C(38)	114(9)
C(27)-C(32)	1.39(13)	C(37)-C(38)-C(39)	112(8)
C(28)-C(29)	1.4(2)	C(40)-C(39)-C(38)	107(10)

C(29)-C(30)	1.4(2)	N(5)-C(40)-C(39)	117(8)
C(30)-C(31)	1.4(2)	N(5)-C(40)-C(35)	104(6)
C(31)-C(32)	1.4(2)	C(39)-C(40)-C(35)	111(7)
P(2)-O(6)	1.48(6)	C(42)-C(41)-C(46)	115(8)
P(2)-N(5)	1.64(7)	C(42)-C(41)-P(2)	121(7)
P(2)-N(4)	1.64(7)	C(46)-C(41)-P(2)	124(6)
P(2)-C(41)	1.81(9)	C(41)-C(42)-C(43)	122(9)
N(4)-C(67)	1.47(11)	C(44)-C(43)-C(42)	121(9)
N(4)-C(35)	1.48(11)	C(43)-C(44)-C(45)	118(9)
N(5)-C(68)	1.46(11)	C(46)-C(45)-C(44)	119(8)
N(5)-C(40)	1.47(10)	C(46)-C(45)-C(48)	107(7)
N(6)-C(54)	1.36(11)	C(44)-C(45)-C(48)	134(8)
N(6)-C(52)	1.40(11)	C(45)-C(46)-O(7)	111(7)
O(7)-C(47)	1.38(9)	C(45)-C(46)-C(41)	124(8)
O(7)-C(46)	1.38(10)	O(7)-C(46)-C(41)	124(7)
O(8)-C(54)	1.36(10)	O(7)-C(47)-C(52)	124(8)
O(8)-C(53)	1.47(9)	O(7)-C(47)-C(48)	112(7)
O(9)-C(54)	1.19(10)	C(52)-C(47)-C(48)	124(7)
C(35)-C(36)	1.51(12)	C(47)-C(48)-C(49)	118(8)
C(35)-C(40)	1.51(11)	C(47)-C(48)-C(45)	105(7)
C(36)-C(37)	1.5(2)	C(49)-C(48)-C(45)	137(8)
C(37)-C(38)	1.5(2)	C(50)-C(49)-C(48)	119(9)
C(38)-C(39)	1.53(14)	C(49)-C(50)-C(51)	122(8)
C(39)-C(40)	1.51(13)	C(52)-C(51)-C(50)	120(8)
C(41)-C(42)	1.39(12)	C(52)-C(51)-C(53)	115(8)
C(41)-C(46)	1.40(11)	C(50)-C(51)-C(53)	125(8)
C(42)-C(43)	1.40(13)	C(51)-C(52)-C(47)	117(8)
C(43)-C(44)	1.37(13)	C(51)-C(52)-N(6)	120(8)
C(44)-C(45)	1.40(12)	C(47)-C(52)-N(6)	123(7)
C(45)-C(46)	1.38(12)	O(8)-C(53)-C(51)	108(7)
C(45)-C(48)	1.44(12)	O(8)-C(53)-C(55)	107(7)
C(47)-C(52)	1.39(12)	C(51)-C(53)-C(55)	113(7)
C(47)-C(48)	1.40(12)	O(8)-C(53)-C(61)	105(6)
C(48)-C(49)	1.40(11)	C(51)-C(53)-C(61)	113(8)
C(49)-C(50)	1.37(13)	C(55)-C(53)-C(61)	112(7)
C(50)-C(51)	1.40(13)	O(9)-C(54)-N(6)	124(8)
C(51)-C(52)	1.38(11)	O(9)-C(54)-O(8)	120(8)
C(51)-C(53)	1.51(12)	N(6)-C(54)-O(8)	115(8)
C(53)-C(55)	1.52(14)	C(56)-C(55)-C(60)	117(9)
C(53)-C(61)	1.53(12)	C(56)-C(55)-C(53)	123(9)
C(55)-C(56)	1.39(12)	C(60)-C(55)-C(53)	120(8)
C(55)-C(60)	1.39(14)	C(57)-C(56)-C(55)	121(10)
C(56)-C(57)	1.4(2)	C(58)-C(57)-C(56)	122(9)
C(57)-C(58)	1.4(2)	C(57)-C(58)-C(59)	119(10)
C(58)-C(59)	1.4(2)	C(58)-C(59)-C(60)	120(10)
C(59)-C(60)	1.4(2)	C(55)-C(60)-C(59)	121(10)
C(61)-C(66)	1.38(12)	C(66)-C(61)-C(62)	118(9)
C(61)-C(62)	1.38(14)	C(66)-C(61)-C(53)	121(8)

C(62)-C(63)	1.4(2)	C(62)-C(61)-C(53)	121(8)
C(63)-C(64)	1.4(2)	C(63)-C(62)-C(61)	120(10)
C(64)-C(65)	1.4(2)	C(64)-C(63)-C(62)	122(10)
C(65)-C(66)	1.38(13)	C(63)-C(64)-C(65)	118(10)
		C(64)-C(65)-C(66)	121(10)
O(1)-P(1)-N(2)	117(4)	C(61)-C(66)-C(65)	121(9)

Table 4: Anisotropic Displacement Parameters ($Å^2$ x 10^3) for (25).

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [h^2 a^* 2 U11 + ... + 2 h k a^* b^* U12]$

Atom	U11	U22	U33	U23	U13	U12
P(1)	35(11)	52(14)	38(10)	-4(11)	-4(9)	-4(11)
N(1)	42(37)	48(43)	51(38)	5(35)	-5(29)	-5(34)
N(2)	43(45)	55(50)	51(41)	16(38)	-10(34)	-8(39)
N(3)	35(38)	59(53)	48(39)	-16(39)	-4(33)	4(40)
O(1)	43(34)	95(54)	38(30)	-16(32)	-2(24)	-1(35)
O(2)	33(31)	52(38)	44(29)	-13(32)	-5(24)	2(31)
O(3)	39(34)	86(53)	43(31)	-16(33)	-3(25)	0(35)
O(4)	59(43)	127(72)	67(38)	-50(51)	5(34)	-1(47)
O(5)	42(34)	57(42)	52(32)	-2(31)	7(26)	6(30)
C(1)	39(46)	56(57)	53(47)	5(44)	3(37)	4(42)
C(2)	48(55)	106(95)	79(66)	36(66)	-3(47)	9(60)
C(3)	48(59)	141(127)	96(83)	55(85)	-10(56)	5(73)
C(4)	35(54)	155(139)	70(64)	30(84)	-19(47)	-10(78)
C(5)	31(45)	85(76)	65(56)	14(53)	-6(39)	-10(46)
C(6)	39(44)	57(63)	43(43)	3(42)	-6(34)	-3(41)
C(7)	39(47)	48(55)	36(40)	3(41)	-3(34)	1(43)
C(8)	44(51)	48(57)	46(47)	-6(45)	-7(39)	-11(46)
C(9)	51(58)	53(62)	64(54)	-21(52)	-4(44)	-7(52)
C(10)	50(57)	47(60)	61(52)	-14(50)	2(43)	7(48)
C(11)	40(49)	38(54)	45(44)	-3(42)	-1(37)	3(42)
C(12)	45(56)	39(53)	35(43)	-1(40)	-4(38)	-6(44)
C(13)	38(47)	49(57)	36(40)	-1(46)	0(34)	0(47)
C(14)	41(50)	39(51)	43(43)	-2(42)	-5(36)	2(44)
C(15)	41(52)	55(65)	56(50)	-11(49)	-2(41)	11(48)
C(16)	29(46)	59(66)	58(52)	-1(50)	-3(39)	12(45)
C(17)	33(42)	49(55)	41(41)	1(41)	-4(34)	3(41)
C(18)	37(47)	52(58)	35(40)	-5(41)	-1(34)	1(43)
C(19)	40(50)	69(69)	38(42)	-5(47)	-1(37)	2(48)
C(20)	42(53)	69(68)	46(47)	-17(50)	4(42)	-7(49)
C(21)	33(47)	70(71)	42(46)	-5(49)	-6(37)	2(47)
C(22)	38(51)	86(83)	54(51)	12(56)	-3(42)	11(56)
C(23)	34(51)	88(85)	74(63)	-1(63)	0(45)	7(54)
C(24)	50(65)	110(112)	89(78)	19(80)	-14(58)	25(73)
C(25)	72(86)	181(173)	89(83)	60(99)	-1(67)	40(98)
C(26)	60(68)	132(116)	76(69)	43(85)	7(54)	15(83)
C(27)	32(45)	63(66)	51(47)	-13(55)	-2(37)	2(49)
C(28)	56(66)	55(72)	72(66)	-13(59)	-14(52)	5(55)
C(29)	62(70)	58(81)	104(90)	-15(72)	-9(61)	-1(59)
C(30)	65(71)	66(84)	102(87)	13(78)	2(64)	0(66)
C(31)	78(81)	83(98)	81(74)	16(75)	-9(61)	-2(76)
C(32)	66(67)	58(71)	59(56)	-2(58)	-6(47)	-8(60)
C(33)	68(70)	52(66)	86(67)	-7(55)	-3(56)	-23(54)

C(34)	49(58)	62(70)	69(58)	11(54)	4(46)	0(52)
P(2)	36(11)	49(14)	37(10)	-2(11)	-2(9)	0(11)
N(4)	33(40)	48(46)	52(40)	7(37)	2(32)	-1(36)
N(5)	35(34)	46(43)	49(37)	2(33)	-8(28)	-6(33)
N(6)	31(38)	63(55)	47(39)	-18(39)	0(34)	1(40)
O(6)	38(32)	82(48)	39(28)	-7(31)	-1(24)	8(31)
O(7)	32(30)	41(36)	43(28)	-7(29)	1(24)	1(28)
O(8)	41(33)	84(51)	36(28)	-8(32)	-3(23)	3(34)
O(9)	51(38)	107(63)	62(36)	-38(44)	2(31)	3(41)
O(10)	46(35)	62(44)	46(31)	-7(31)	3(27)	4(31)
C(35)	36(41)	55(54)	47(43)	5(45)	-1(35)	1(42)
C(36)	52(58)	92(79)	67(60)	4(59)	-19(46)	-25(57)
C(37)	60(71)	122(120)	98(80)	39(91)	-37(63)	-25(84)
C(38)	71(72)	136(117)	88(76)	57(84)	-40(60)	-24(80)
C(39)	60(61)	65(69)	81(63)	37(56)	-7(50)	-3(53)
C(40)	36(44)	60(60)	41(40)	1(41)	-1(33)	-6(42)
C(41)	42(49)	36(50)	38(42)	3(40)	-2(35)	-6(42)
C(42)	56(59)	46(57)	49(48)	-8(46)	-2(43)	0(49)
C(43)	68(68)	44(58)	58(53)	-16(48)	-1(47)	-7(53)
C(44)	54(60)	49(64)	62(52)	-15(51)	7(46)	0(50)
C(45)	43(51)	40(57)	45(46)	-3(43)	3(39)	2(45)
C(46)	39(51)	35(50)	38(42)	1(40)	-1(37)	2(42)
C(47)	25(41)	48(57)	39(38)	0(45)	-1(32)	4(43)
C(48)	40(48)	44(54)	40(41)	-2(43)	-1(36)	6(46)
C(49)	50(57)	46(59)	55(51)	-12(47)	4(43)	7(48)
C(50)	38(48)	54(64)	52(48)	-5(46)	0(41)	8(47)
C(51)	40(49)	51(56)	38(41)	0(41)	-4(36)	7(43)
C(52)	38(48)	54(58)	36(40)	0(43)	0(35)	4(45)
C(53)	33(45)	54(58)	39(41)	-5(42)	-1(34)	1(42)
C(54)	44(53)	70(69)	43(45)	-11(50)	3(41)	0(50)
C(55)	32(44)	56(63)	50(46)	1(50)	-3(37)	9(47)
C(56)	62(63)	65(78)	46(49)	0(53)	-7(42)	-2(57)
C(57)	87(81)	64(80)	57(57)	9(60)	-10(53)	2(68)
C(58)	81(80)	62(83)	90(83)	16(71)	-9(64)	-2(68)
C(59)	52(62)	58(76)	99(84)	1(69)	-9(56)	-2(55)
C(60)	44(57)	75(85)	58(57)	-10(60)	-9(44)	1(54)
C(61)	40(49)	58(64)	45(46)	-3(46)	-6(38)	-4(47)
C(62)	55(66)	133(119)	82(70)	52(85)	11(56)	18(78)
C(63)	66(79)	174(165)	108(90)	81(105)	5(70)	42(93)
C(64)	47(67)	122(117)	97(85)	23(90)	-12(62)	16(78)
C(65)	40(57)	87(86)	80(69)	7(68)	2(50)	3(58)
C(66)	45(54)	67(69)	52(51)	1(50)	-1(43)	2(53)
C(67)	55(60)	42(59)	90(68)	23(55)	8(51)	-1(50)
C(68)	55(60)	59(68)	79(65)	3(54)	3(50)	-8(52)

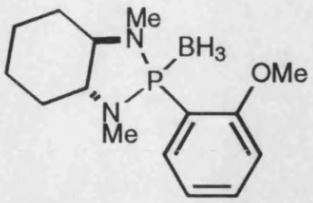
Table 5: Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2$ x 10^3) for (25)

Atom	x	y	z	U(eq)
H(3)	-3401(85)	-5006(713)	-6959(654)	57
H(51)	-2245(195)	-4547(525)	-8201(564)	60
H(52)	-2195(199)	-3986(696)	-7161(358)	60
H(1)	-1751(22)	-4862(77)	-4290(67)	59
H(2A)	-1793(25)	-5733(105)	-2653(79)	93
H(2B)	-1819(25)	-4679(105)	-2048(79)	93
H(3A)	-1220(28)	-5202(121)	-1908(100)	115
H(3B)	-1220(28)	-5328(121)	-3159(100)	115
H(4A)	-942(25)	-3792(129)	-2687(82)	105
H(4B)	-1269(25)	-3438(129)	-2069(82)	105
H(5A)	-1292(21)	-2561(87)	-3710(70)	73
H(5B)	-1268(21)	-3597(87)	-4349(70)	73
H(6)	-1837(20)	-3069(72)	-3074(64)	56
H(8)	-2428(24)	-2063(76)	-3272(61)	56
H(9)	-2878(24)	-1121(82)	-2623(72)	68
H(10)	-3460(24)	-1310(74)	-3341(68)	63
H(15)	-4110(23)	-2077(79)	-4536(66)	61
H(16)	-4503(24)	-3064(78)	-5618(68)	59
H(22)	-5002(24)	-4782(89)	-6039(71)	72
H(23)	-5546(25)	-4083(98)	-6546(83)	78
H(24)	-5613(31)	-3107(114)	-8069(99)	101
H(25)	-5140(33)	-2878(147)	-9111(100)	137
H(26)	-4593(30)	-3570(127)	-8605(88)	107
H(28)	-4659(28)	-6476(91)	-7580(90)	75
H(29)	-4722(30)	-8012(99)	-6765(98)	90
H(30)	-4526(31)	-8259(102)	-5002(104)	93
H(31)	-4256(31)	-6918(111)	-4064(91)	98
H(32)	-4190(27)	-5341(90)	-4877(75)	74
H(33A)	-2432(156)	-5767(263)	-3273(142)	103
H(33B)	-2331(112)	-5901(212)	-4465(424)	103
H(33C)	-2681(51)	-5326(104)	-4214(524)	103
H(34A)	-2014(109)	-1996(246)	-5847(246)	90
H(34B)	-1623(50)	-2111(209)	-5356(425)	90
H(34C)	-1901(149)	-1491(94)	-4738(201)	90
H(6)	-6586(233)	-9203(754)	-7929(682)	57
H(101)	-2782(186)	-4931(614)	-6530(533)	62
H(102)	-2846(208)	-5473(714)	-7676(388)	62
H(35)	-8439(21)	-10378(78)	-10382(60)	56
H(36A)	-8722(25)	-11776(94)	-11264(77)	85
H(36B)	-8456(25)	-11702(94)	-12185(77)	85
H(37A)	-8951(30)	-10168(115)	-11680(97)	114
H(37B)	-8970(30)	-10810(115)	-12743(97)	114
H(38A)	-8759(31)	-9122(119)	-13022(92)	120

H(38B)	-8486(31)	-9950(119)	-13365(92)	120
H(39A)	-8164(26)	-8711(85)	-12368(84)	83
H(39B)	-8418(26)	-8807(85)	-11419(84)	83
H(40)	-7987(20)	-10427(72)	-12105(61)	55
H(42)	-7605(26)	-12339(77)	-11556(66)	61
H(43)	-7145(27)	-13252(79)	-12232(70)	68
H(44)	-6566(25)	-13010(76)	-11577(69)	66
H(49)	-5906(24)	-12167(78)	-10416(67)	61
H(50)	-5523(24)	-11157(77)	-9384(67)	58
H(56)	-5823(26)	-8917(87)	-10166(70)	70
H(57)	-5756(30)	-7376(96)	-11002(77)	84
H(58)	-5497(32)	-6015(102)	-10121(98)	94
H(59)	-5308(28)	-6170(93)	-8331(94)	84
H(60)	-5384(26)	-7710(92)	-7443(83)	71
H(62)	-5435(29)	-10677(120)	-6418(89)	108
H(63)	-4893(33)	-11366(146)	-5919(108)	140
H(64)	-4421(31)	-11213(126)	-6971(103)	107
H(65)	-4485(27)	-10206(98)	-8482(88)	83
H(66)	-5016(24)	-9415(85)	-8961(70)	66
H(67A)	-8253(153)	-12804(199)	-10045(94)	93
H(67B)	-8366(109)	-11972(159)	-9227(370)	93
H(67C)	-7983(51)	-12445(338)	-9114(337)	93
H(68A)	-7652(45)	-8347(127)	-11096(492)	97
H(68B)	-7441(127)	-9184(264)	-11691(271)	97
H(68C)	-7347(89)	-8960(348)	-10472(260)	97

APPENDIX:

CHAPTER 4: X-RAY STRUCTURE OF DIAZAPHOSPHOLIDINE BORANE COMPLEX (32)



The structure of (**32**) is shown in fig. 1.

Fig. 1:

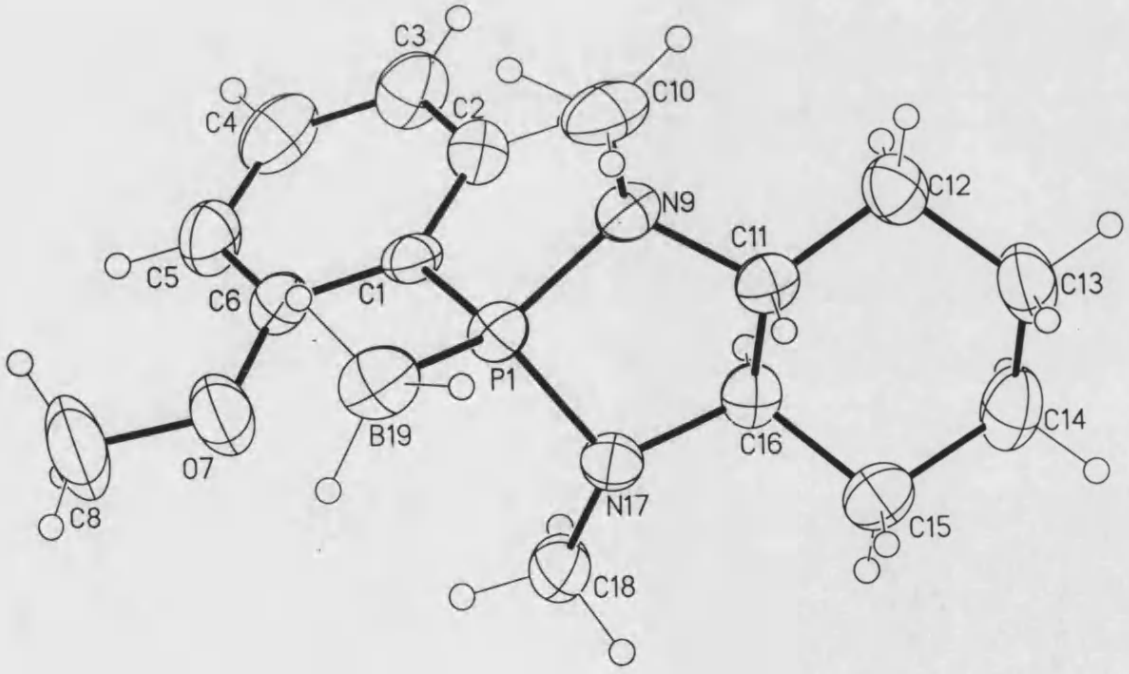


Table 1: Crystal Data and Structure Refinement for (**32**)

Empirical formula	$C_{15}H_{26}BN_2OP$
Formula weight	292.16
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.300(4) Å alpha = 90°
	b = 13.789(5) Å beta = 90°
	c = 14.553(5) Å gamma = 90°
Volume, Z	1665.6(11) $Å^3$, 4
Density (calculated)	1.165 Mg/m^3
Absorption coefficient	0.163 mm^{-1}
F(000)	632
Crystal size	0.2 x 0.2 x 0.16 mm
θ range for data collection	2.03 to 24.00°
Limiting indices	$-9 \le h \le 11$, $-12 \le k \le 18$, $-19 \le l \le 19$
Reflections collected	7586
Independent reflections	2605 (R_{int} = 0.0852)
Absorption correction	Psi-scan
Max. and min. transmission	0.68 and 0.61
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2605 / 0 / 193
Goodness-of-fit on F^2	1.068
Final R indices [I>2σ(I)]	R1 = 0.0637, wR2 = 0.0973
R indices (all data)	R1 = 0.1065, wR2 = 0.1124
Absolute structure parameter	0.2(2)
Largest diff. peak and hole	0.207 and -0.281 $eÅ^{-3}$

Table 2: Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for **(32)**. Ueq is defined as one third of the trace of the orthogonalised Uij tensor.

	x	y	z	U(eq)
P(1)	7683.5(13)	9302.3(8)	7786.4(8)	33(1)
C(1)	7629(5)	8171(3)	8432(3)	32(1)
C(2)	9030(5)	7813(3)	8835(3)	41(1)
C(3)	9035(7)	6930(3)	9295(3)	49(1)
C(4)	7645(7)	6398(3)	9345(3)	52(1)
C(5)	6238(6)	6723(3)	8958(3)	47(1)
C(6)	6230(6)	7630(3)	8522(3)	38(1)
O(7)	4862(4)	8030(2)	8174(2)	57(1)
C(8)	3464(6)	7437(4)	8077(5)	88(2)
N(9)	9678(4)	9482(2)	7614(2)	34(1)
C(10)	10343(5)	9270(4)	6708(3)	55(1)
C(11)	10140(5)	10413(3)	8029(3)	34(1)
C(12)	11904(5)	10511(3)	8307(3)	44(1)
C(13)	12124(5)	11506(3)	8754(4)	53(1)
C(14)	10955(6)	11684(4)	9539(3)	51(2)
C(15)	9212(5)	11522(3)	9265(3)	43(1)
C(16)	9074(5)	10511(3)	8857(3)	33(1)
N(17)	7468(4)	10237(2)	8514(2)	33(1)
C(18)	6181(5)	10177(3)	9200(3)	44(1)
B(19)	6358(8)	9386(5)	6726(4)	50(2)

Table 3: Bond Lengths [Å] and Angles [°] for (32)

P(1)-N(17)	1.678(3)	P(1)-N(9)	1.693(3)
P(1)-C(1)	1.822(4)	P(1)-B(19)	1.898(6)
C(1)-C(6)	1.386(6)	C(1)-C(2)	1.393(6)
C(2)-C(3)	1.389(6)	C(3)-C(4)	1.370(6)
C(4)-C(5)	1.373(6)	C(5)-C(6)	1.402(6)
C(6)-O(7)	1.360(5)	O(7)-C(8)	1.426(5)
N(9)-C(10)	1.459(5)	N(9)-C(11)	1.469(5)
C(11)-C(16)	1.501(5)	C(11)-C(12)	1.525(5)
C(12)-C(13)	1.530(6)	C(13)-C(14)	1.518(6)
C(14)-C(15)	1.517(6)	C(15)-C(16)	1.519(6)
C(16)-N(17)	1.473(5)	N(17)-C(18)	1.464(5)
B(19)-H(19A)	1.15(4)	B(19)-H(19B)	1.09(4)
B(19)-H(19C)	1.15(4)		

N(17)-P(1)-N(9)	94.9(2)	N(17)-P(1)-C(1)	109.3(2)
N(9)-P(1)-C(1)	103.1(2)	N(17)-P(1)-B(19)	113.9(2)
N(9)-P(1)-B(19)	115.9(2)	C(1)-P(1)-B(19)	117.2(3)
C(6)-C(1)-C(2)	118.0(4)	C(6)-C(1)-P(1)	122.0(4)
C(2)-C(1)-P(1)	120.0(3)	C(3)-C(2)-C(1)	121.1(4)
C(4)-C(3)-C(2)	119.5(5)	C(3)-C(4)-C(5)	121.3(4)
C(4)-C(5)-C(6)	118.8(4)	O(7)-C(6)-C(1)	116.5(4)
O(7)-C(6)-C(5)	122.3(4)	C(1)-C(6)-C(5)	121.2(5)
C(6)-O(7)-C(8)	118.9(4)	O(7)-C(8)-H(8C)	109.5(3)
C(10)-N(9)-C(11)	116.6(4)	C(10)-N(9)-P(1)	118.3(3)
C(11)-N(9)-P(1)	108.8(2)	N(9)-C(11)-C(16)	104.8(3)
N(9)-C(11)-C(12)	115.9(3)	C(16)-C(11)-C(12)	110.1(3)
C(11)-C(12)-C(13)	107.9(3)	C(14)-C(13)-C(12)	112.9(4)
C(15)-C(14)-C(13)	112.8(4)	C(14)-C(15)-C(16)	108.0(4)
N(17)-C(16)-C(11)	103.7(3)	N(17)-C(16)-C(15)	115.9(3)
C(11)-C(16)-C(15)	110.6(3)	C(18)-N(17)-C(16)	116.3(3)
C(18)-N(17)-P(1)	117.6(3)	C(16)-N(17)-P(1)	108.3(3)

Table 4: Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for (**32**).

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U11 + ... + 2 h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
P(1)	38(1)	30(1)	32(1)	0(1)	-1(1)	1(1)
C(1)	33(3)	28(2)	34(3)	-5(2)	8(2)	4(2)
C(2)	39(3)	38(3)	46(3)	-5(3)	-3(3)	-1(2)
C(3)	62(4)	37(3)	48(3)	7(3)	-11(3)	3(3)
C(4)	81(4)	35(3)	41(3)	4(2)	8(3)	-3(3)
C(5)	50(3)	37(3)	55(4)	2(3)	5(3)	-12(3)
C(6)	40(3)	32(3)	40(3)	-6(2)	1(3)	-2(2)
O(7)	39(2)	48(2)	84(3)	11(2)	-10(2)	-8(2)
C(8)	48(3)	77(4)	138(6)	9(4)	-24(4)	-25(3)
N(9)	41(2)	29(2)	33(2)	0(2)	11(2)	-2(2)
C(10)	66(3)	47(3)	51(3)	-9(3)	19(3)	10(3)
C(11)	39(3)	30(3)	33(3)	4(2)	3(2)	2(2)
C(12)	40(3)	42(3)	49(3)	7(2)	3(2)	-5(2)
C(13)	39(3)	45(3)	73(4)	7(3)	-10(3)	-11(3)
C(14)	60(4)	42(3)	50(4)	-2(3)	-20(3)	-6(3)
C(15)	51(3)	39(3)	37(3)	0(2)	1(3)	3(3)
C(16)	38(3)	28(3)	32(3)	8(2)	-5(2)	0(2)
N(17)	33(2)	37(2)	29(2)	-2(2)	6(2)	0(2)
C(18)	40(3)	45(3)	46(3)	-12(2)	6(3)	-7(2)
B(19)	62(4)	48(4)	39(3)	3(3)	-13(3)	13(4)

Table 5: Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2$ x 10^3) for (32)

	x	y	z	U(eq)
H(2A)	9997	8179	8795	49
H(3A)	9997	6697	9572	59
H(4A)	7655	5791	9655	63
H(5A)	5286	6341	8984	57
H(8A)	2599	7815	7791	131
H(8B)	3114	7213	8684	131
H(8C)	3718	6877	7689	131
H(10A)	11522	9277	6740	82
H(10B)	9977	9761	6269	82
H(10C)	9977	8628	6507	82
H(11A)	9872	10944	7587	41
H(12A)	12606	10453	7760	52
H(12B)	12198	9992	8746	52
H(13A)	13240	11559	8990	63
H(13B)	11973	12015	8282	63
H(14A)	11226	11246	10055	61
H(14B)	11083	12359	9758	61
H(15A)	8877	12013	8807	51
H(15B)	8504	11581	9809	51
H(16A)	9420	10027	9329	39
H(18A)	5960	10825	9446	65
H(18B)	6518	9747	9700	65
H(18C)	5204	9918	8912	65
H(19A)	6961(47)	10026(32)	6349(31)	74
H(19B)	6441(52)	8662(32)	6423(31)	74
H(19C)	5069(53)	9533(31)	6971(31)	74

APPENDIX:

CHAPTER 5: NMR TITRATION DATA TABLES

Table 1:

Data for the determination of a CAC value for (**24**) in $CDCl_3$ solution. (1ml samples, 20°C, TMS as reference, 400MHz).

Sample Number	Concentration (M)	NH (ppm)
1	$1.48x10^{-2}$	8.71
2	$7.40x10^{-3}$	8.66
3	$3.70x10^{-3}$	8.31
4	$1.85x10^{-3}$	8.18
5	$9.25x10^{-4}$	8.17
6	$4.63x10^{-4}$	7.97

Table 2:

Data for the NMR titration of (**24**) against N-Boc-Glycine in $CDCl_3$ solution. (1ml samples at a concentration of $1.48x10^{-3}$M, 20°C, TMS as reference, 400 and 160MHz).

Sample	Host-Guest ratio	δNH (ppm)	ΔδNH (ppm)	δP (ppm)	ΔδP (ppm)
1	1:0	7.55	0	26.498	0
2	1:1	7.98	0.43	27.074	0.576
3	1:2	8.13	0.58	27.416	0.918
4	1:5	8.28	0.73	27.784	1.286
5	1:10	8.42	0.87	28.053	1.555
6	1:20	8.51	0.96	28.286	1.788
7	1:30	8.56	1.01	28.396	1.898

Table 3:

Data for the NMR titration of (**25**) against N-Boc-Glycine in $CDCl_3$ solution. (1ml samples at a concentration of $1.74x10^{-3}$M, 20°C, TMS as reference, 400 and 160MHz).

Sample	Host-Guest ratio	δNH (ppm)	ΔδNH (ppm)	δP (ppm)	ΔδP (ppm)
1	1:0	8.44	0	29.767	0
2	1:1	8.96	0.52	30.833	1.066
3	1:2	9.17	0.73	31.384	1.617
4	1:5	9.33	0.89	31.776	2.009
5	1:10	9.42	0.98	31.984	2.217
6	1:20	9.43	0.99	32.094	2.327
7	1:30	9.43	0.99	32.229	2.462

Table 4:

Data for the NMR titration of (**25**) against N-Boc-D-Alanine in $CDCl_3$ solution. (1ml samples at a concentration of $1.74x10^{-3}$M, 24°C, TMS as reference, 160MHz).

Sample	Host-Guest ratio	δP (ppm)	ΔδP (ppm)
1	1:0	29.914	0
2	1:1	30.723	0.809
3	1:2	31.004	1.090
4	1:3	31.249	1.335
5	1:4	31.335	1.421
6	1:5	31.482	1.568
7	1:10	31.567	1.653
8	1:20	31.616	1.702
9	1:30	31.519	1.605

Table 5:

Data for the NMR titration of (**25**) against N-Boc-L-Alanine in $CDCl_3$ solution. (1ml samples at a concentration of $1.74x10^{-3}$M, 22°C, TMS as reference, 160MHz).

Sample	Host-Guest ratio	δP (ppm)	ΔδP (ppm)
1	1:0	29.608	0
2	1:1	30.319	0.771
3	1:2	30.612	1.004
4	1:3	30.759	1.151
5	1:4	30.943	1.335
6	1:5	30.919	1.311
7	1:10	31.065	1.457
8	1:20	31.482	1.874
9	1:30	31.567	1.959